

1/38

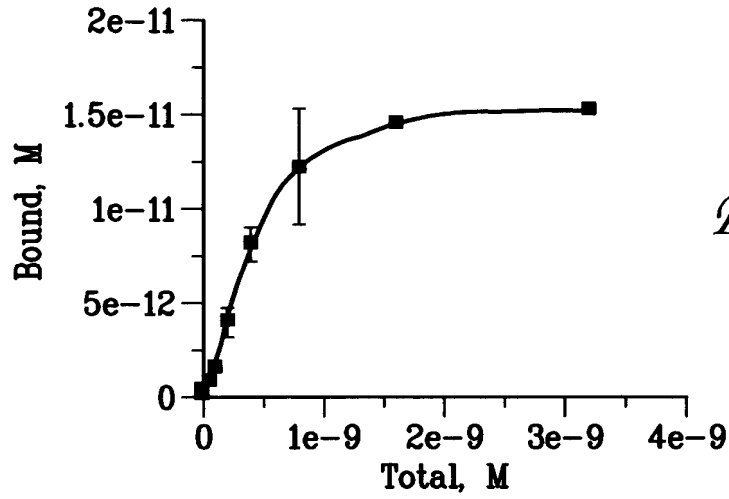


FIG. 1A

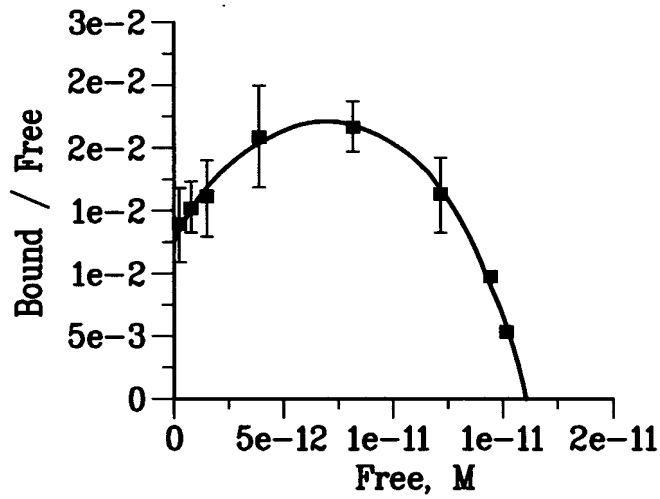


FIG. 1B

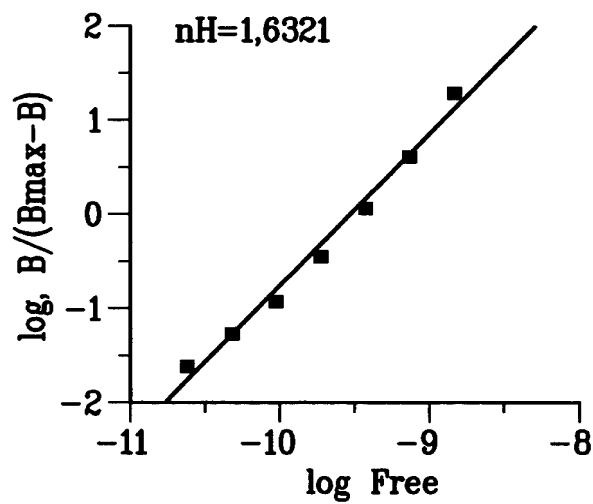


FIG. 1C

2/38

7

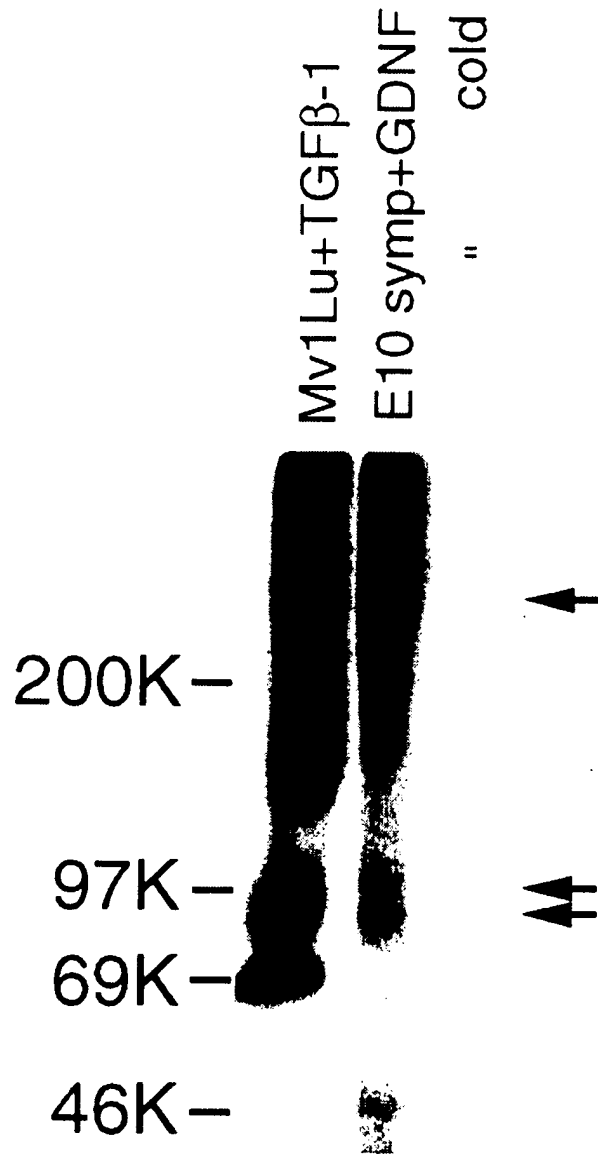
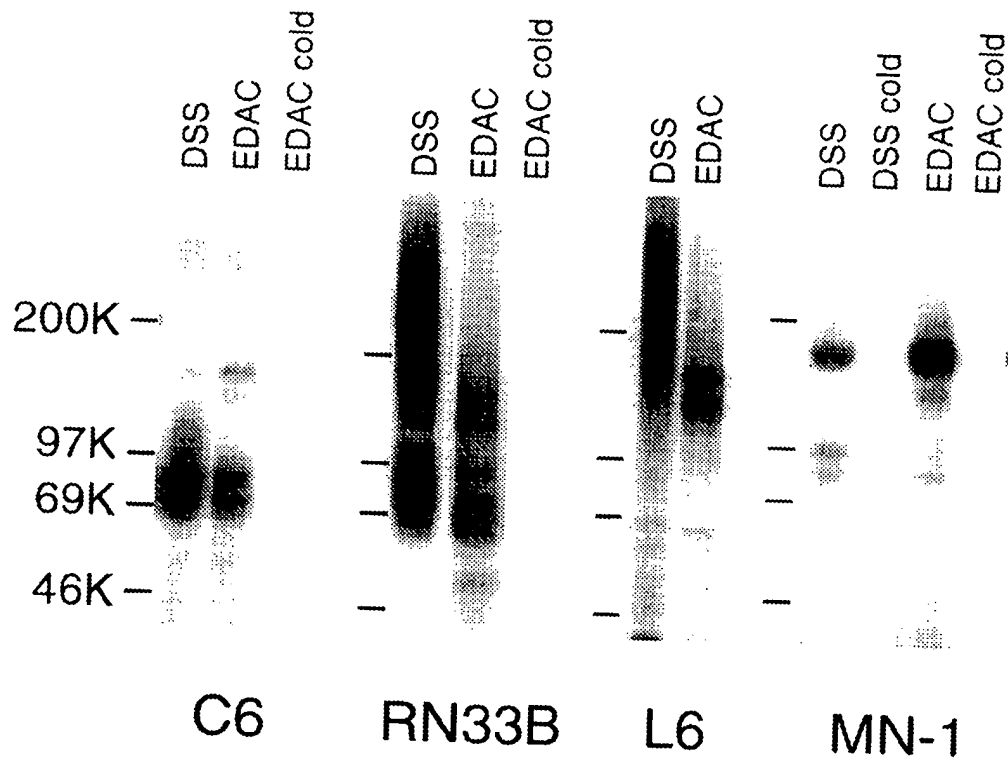


FIG. 2

3/38

7



*FIG. 3*

4/38

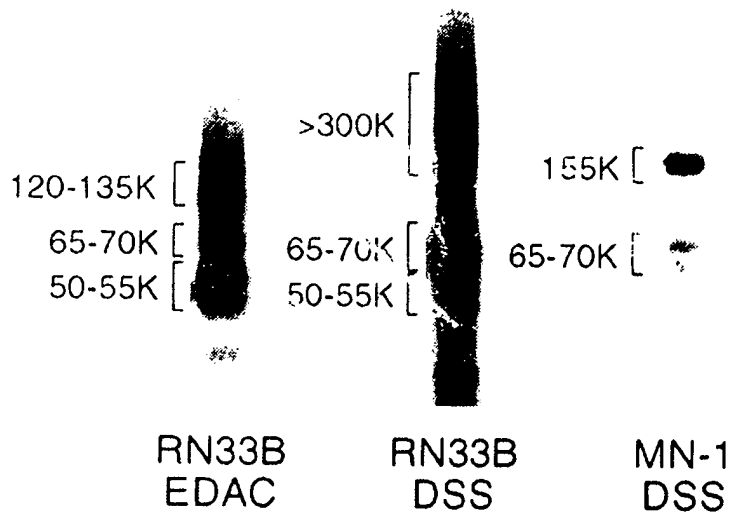


FIG. 4A

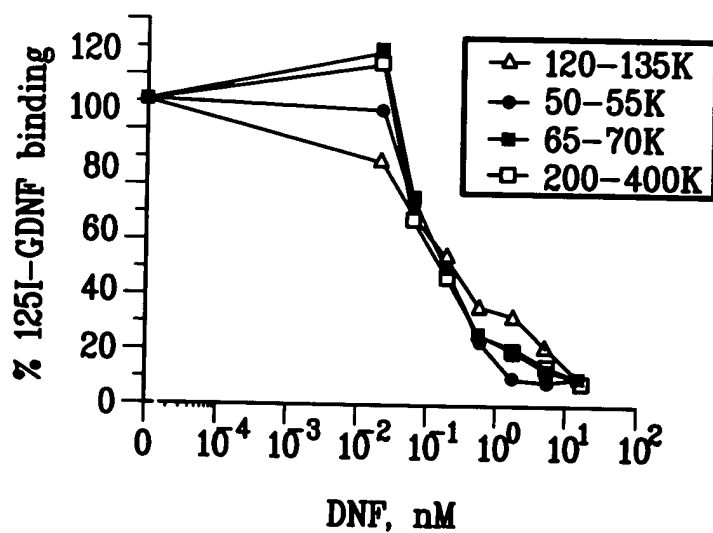


FIG. 4B

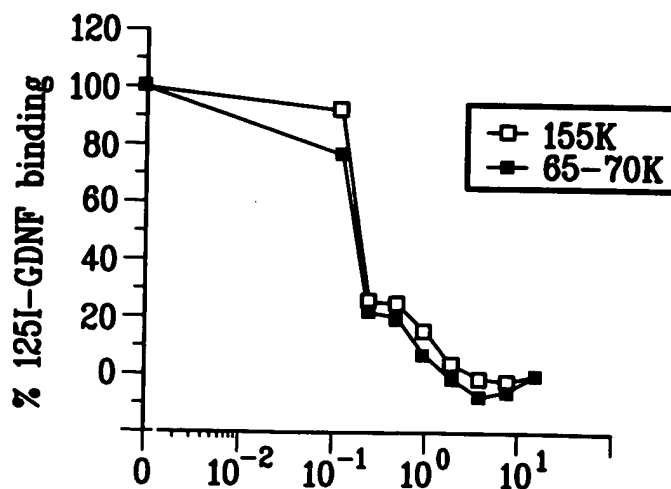


FIG. 4C

5/38

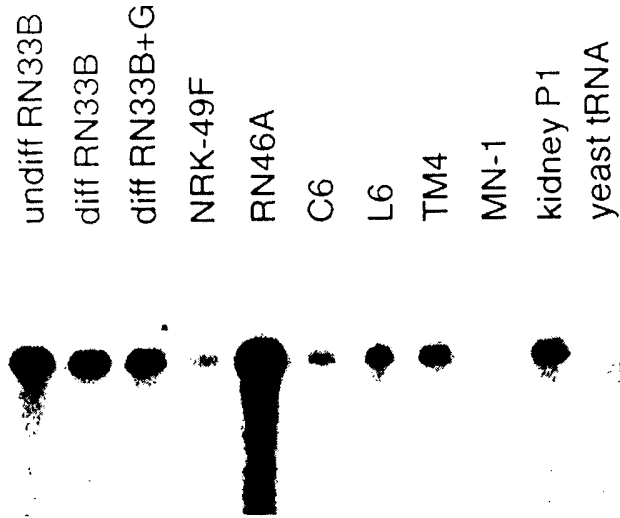


FIG. 5A

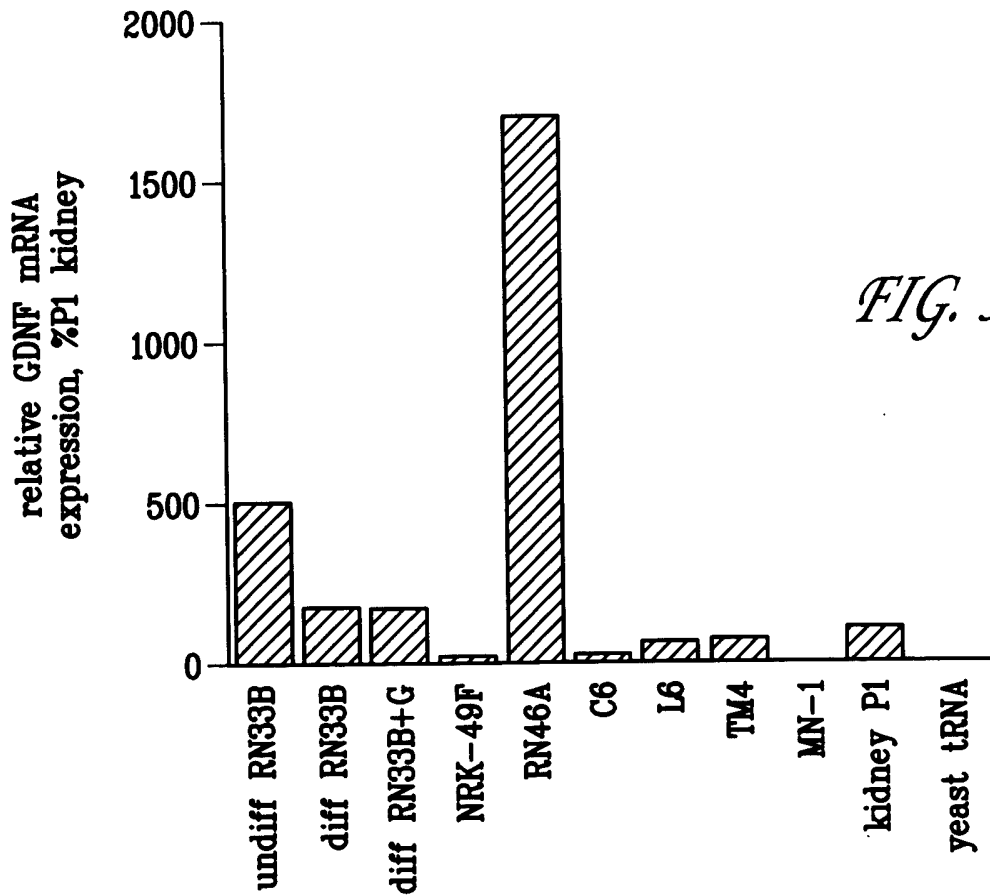
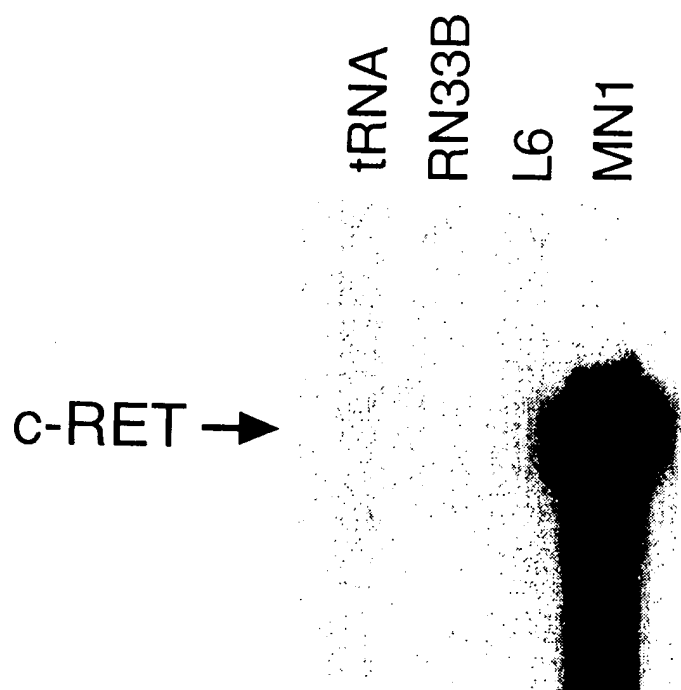


FIG. 5B

6/38

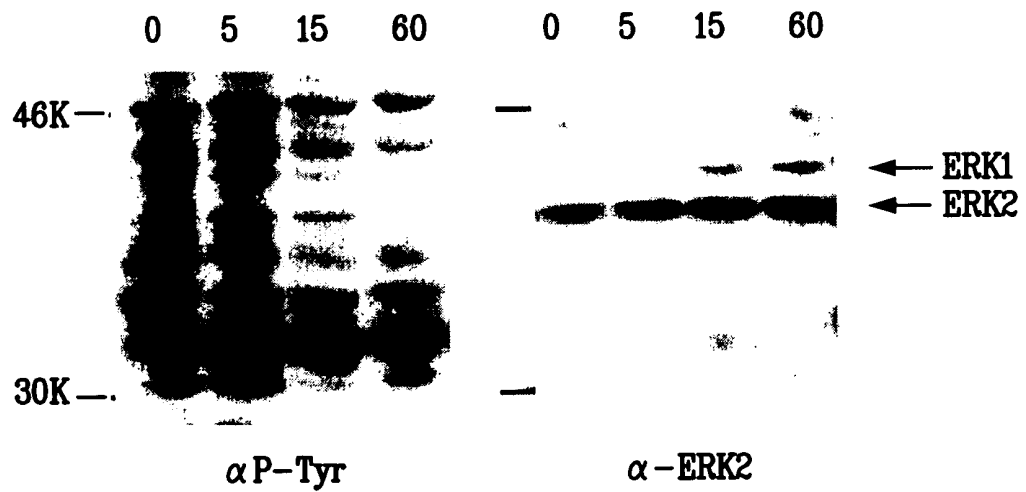
7



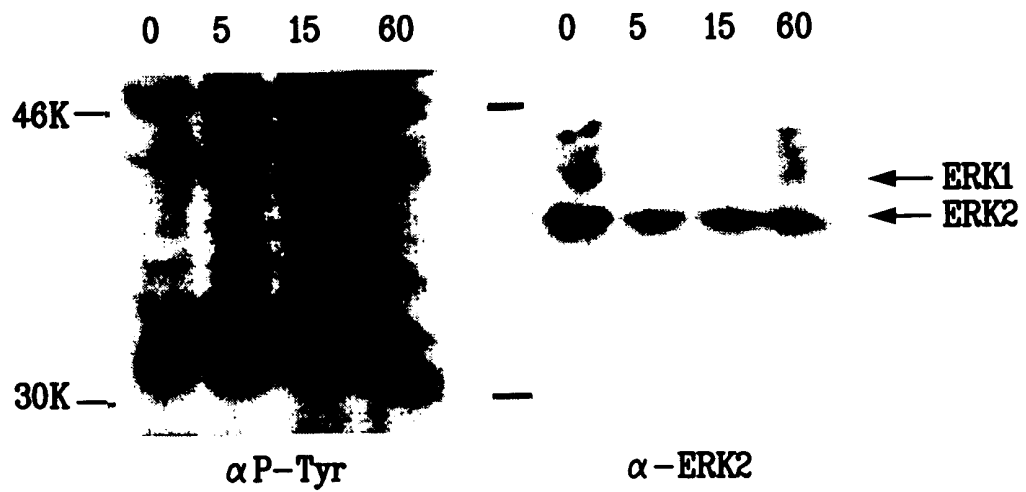
*FIG. 6*

7/38

*FIG. 7A*

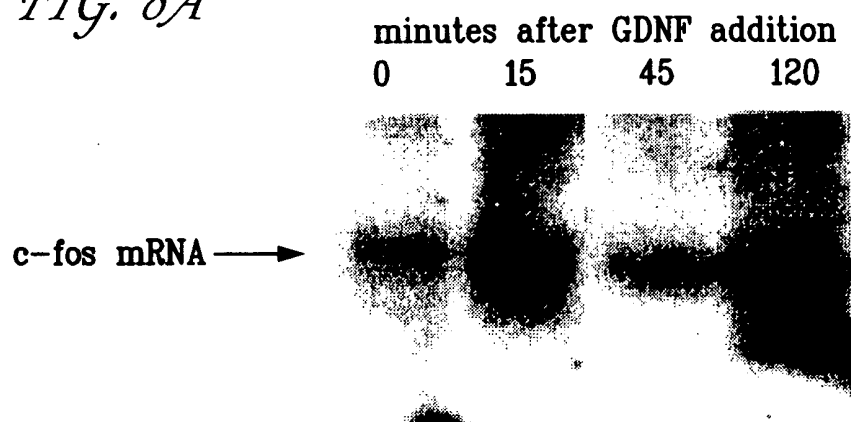


*FIG. 7B*

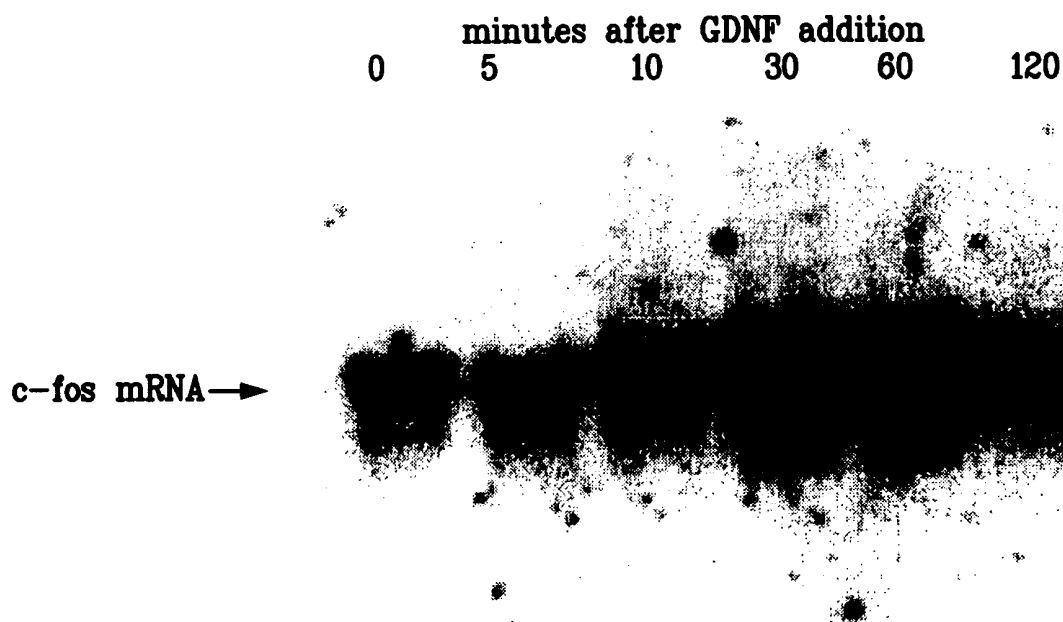


8/38

*FIG. 8A*



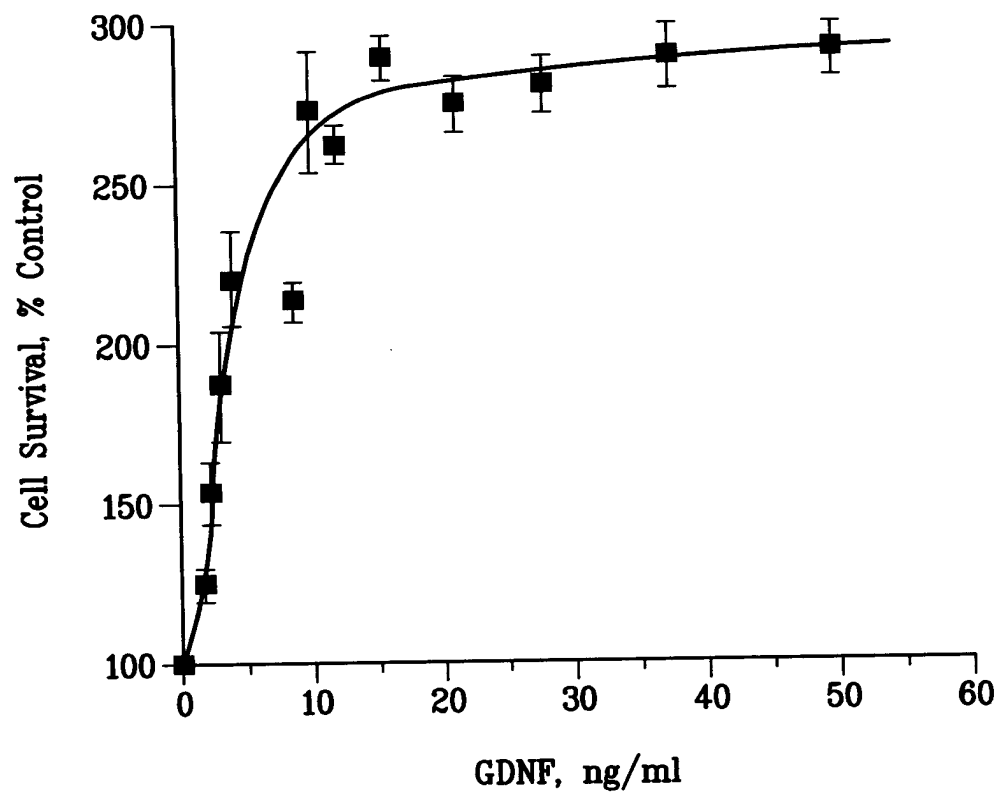
*FIG. 8B*



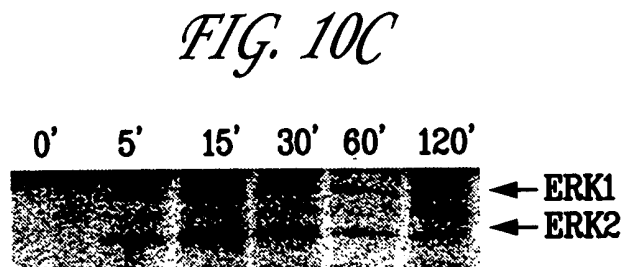
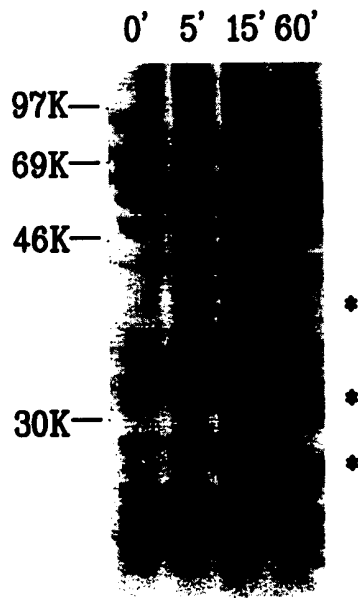
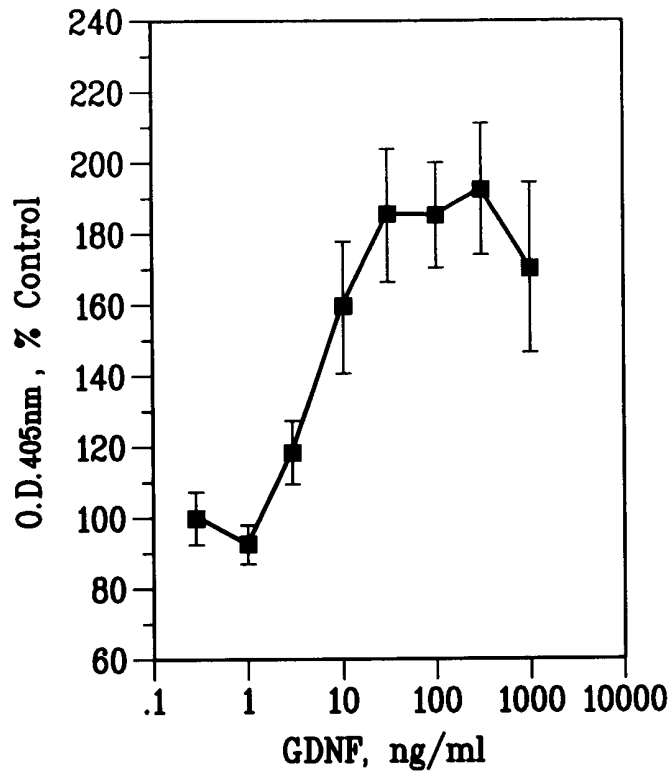


9/38

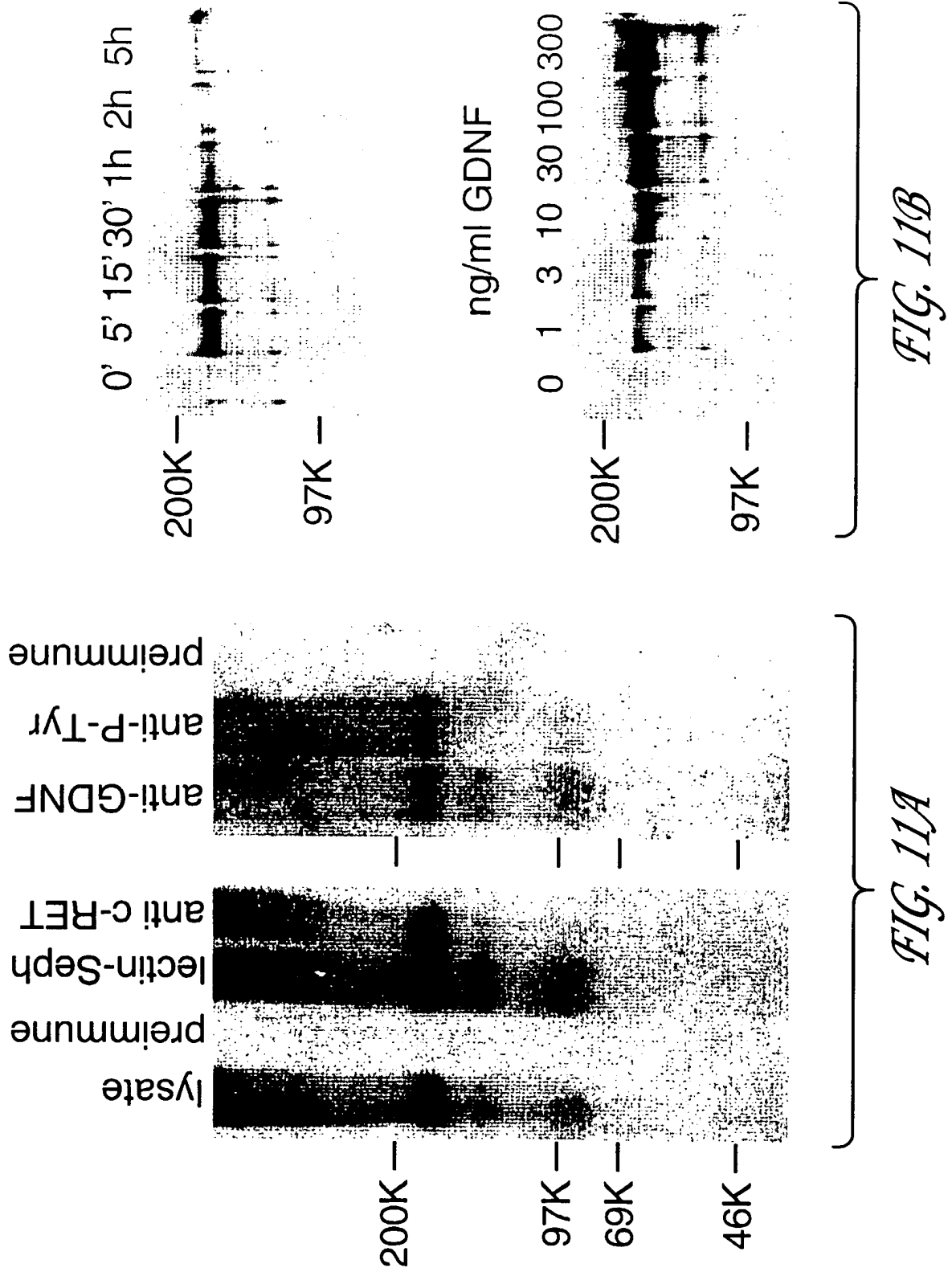
*FIG. 9*



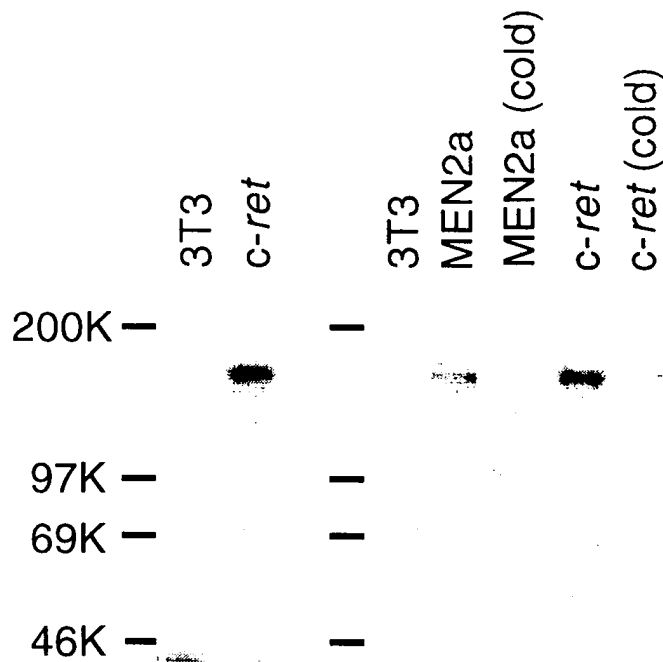
10/38



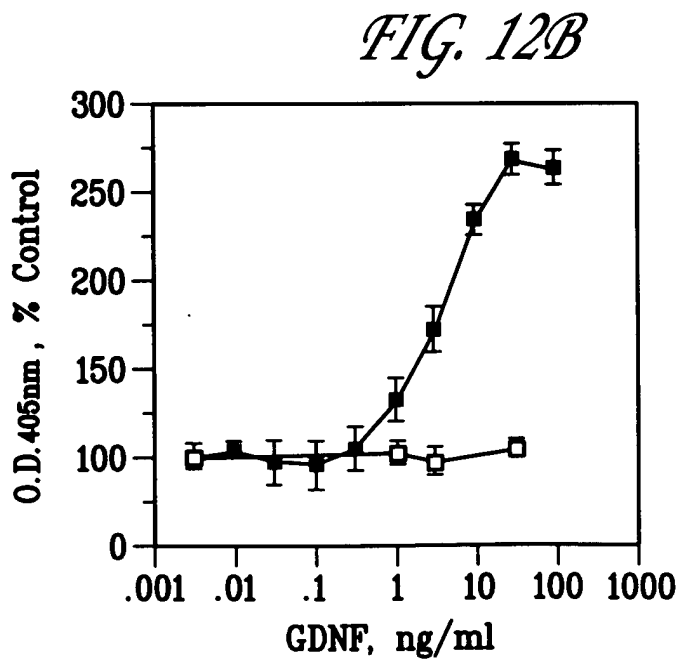
11/38



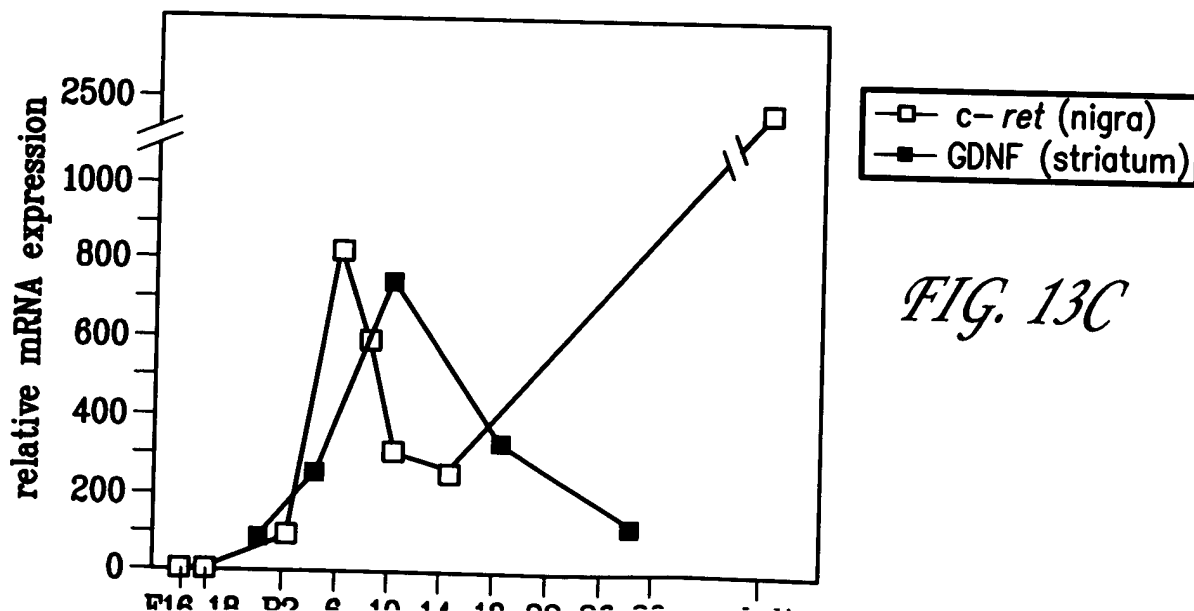
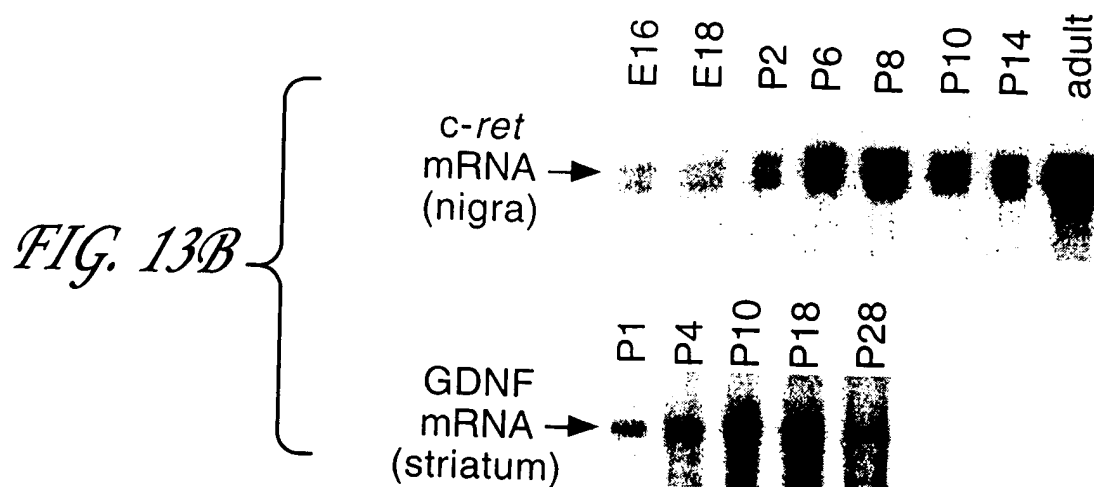
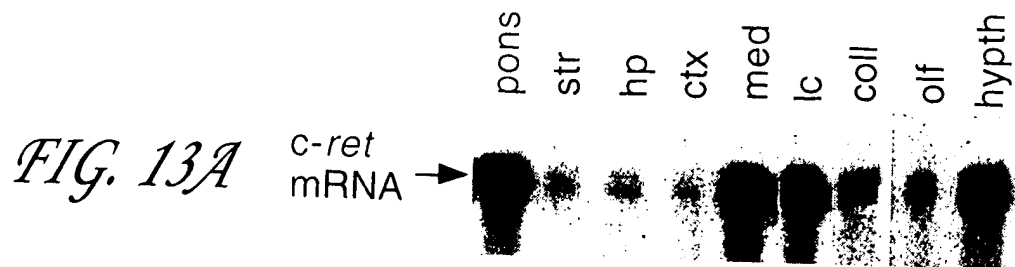
12/38



*FIG. 12A*

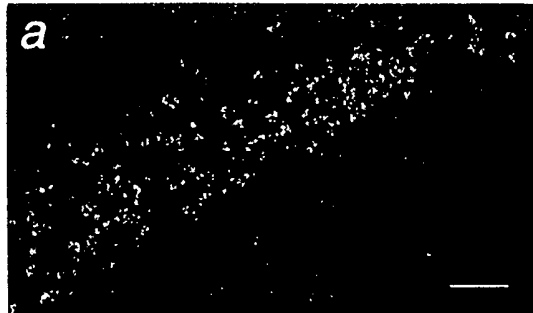


13/38

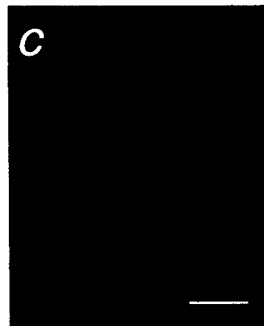
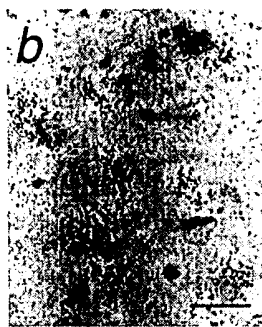
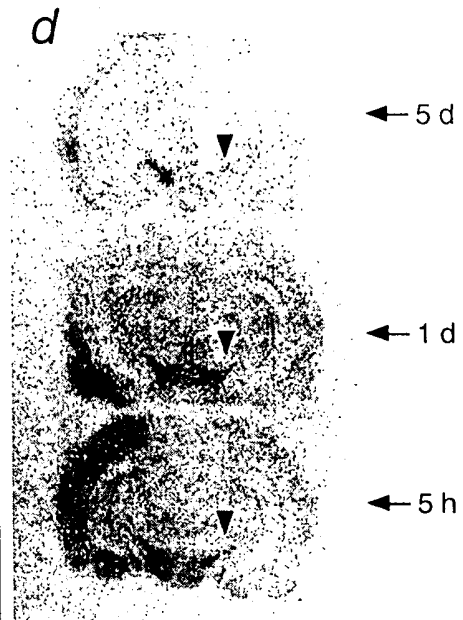


14/38

*FIG. 14A*



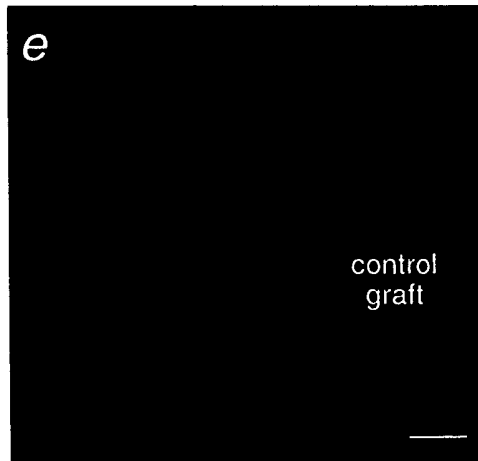
*FIG. 14D*



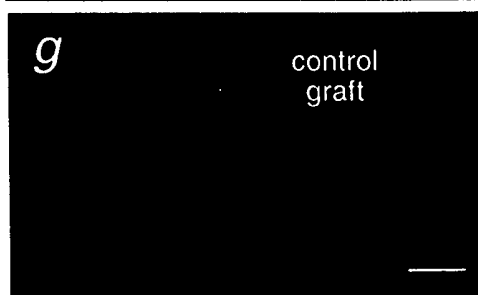
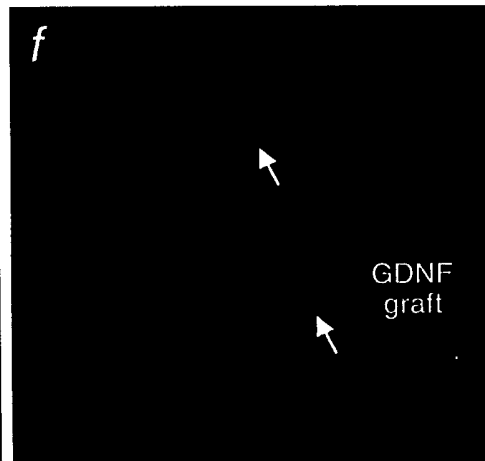
*FIG. 14B*

*FIG. 14C*

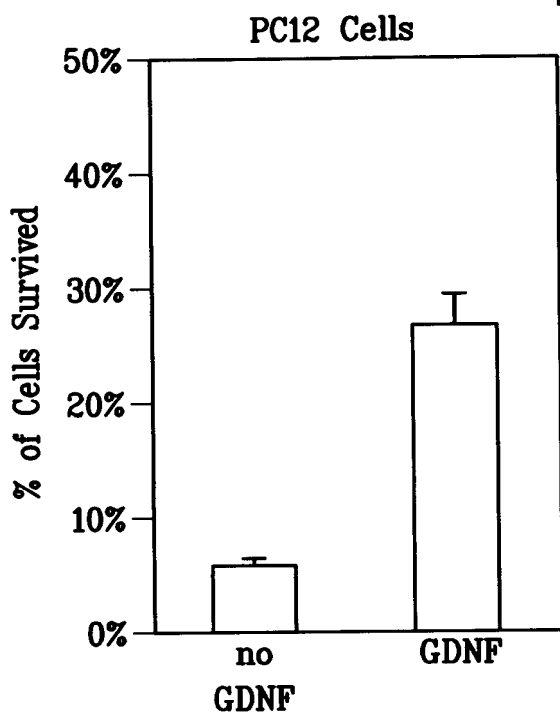
*FIG. 14E*



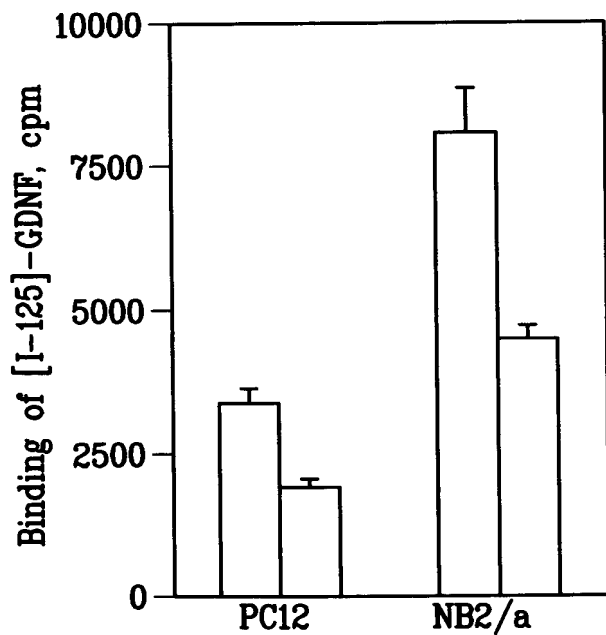
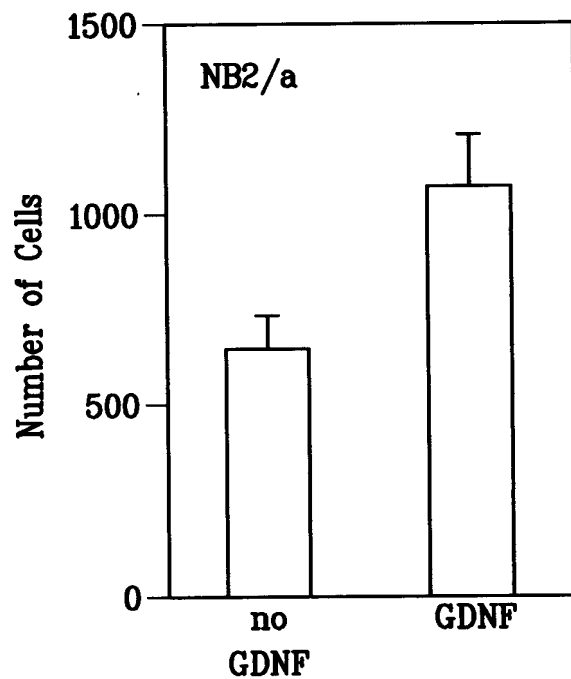
*FIG. 14F*



15/38

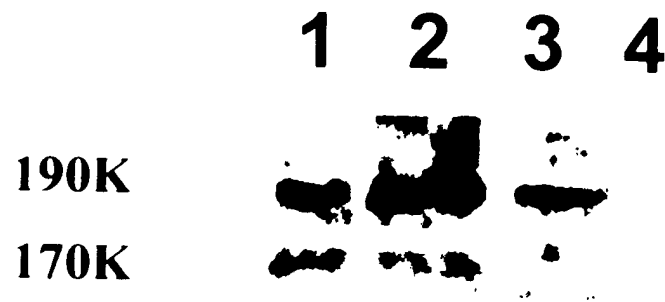


*FIG. 15A*



*FIG. 15C*

16/38

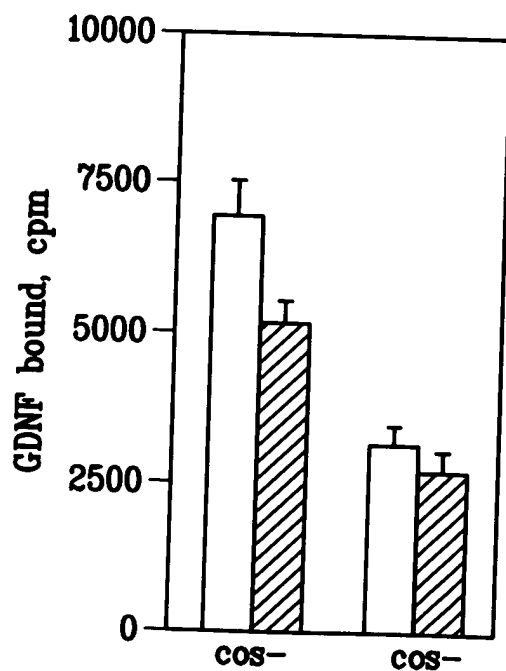
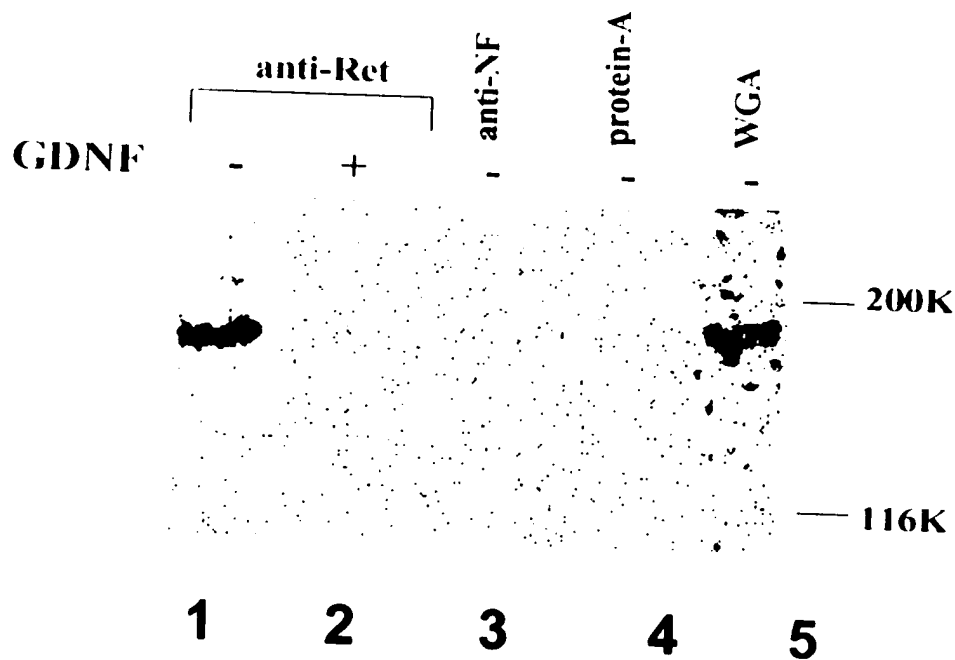


*FIG. 16*



17/38

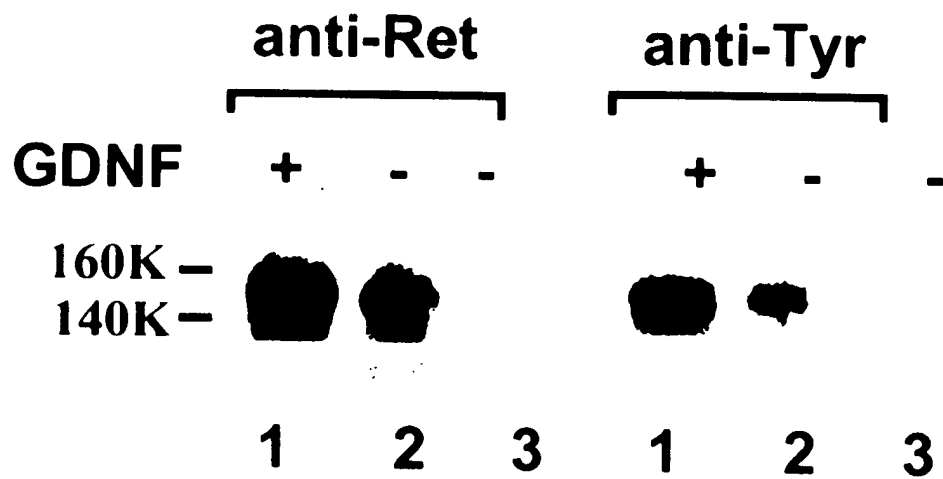
*FIG. 17A*



*FIG. 17B*

18/38

7

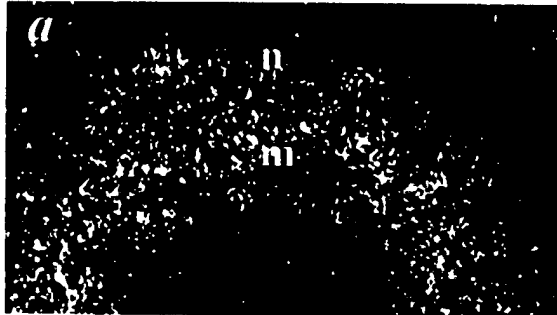


*FIG. 18*

19/38

7

*FIG. 19A*



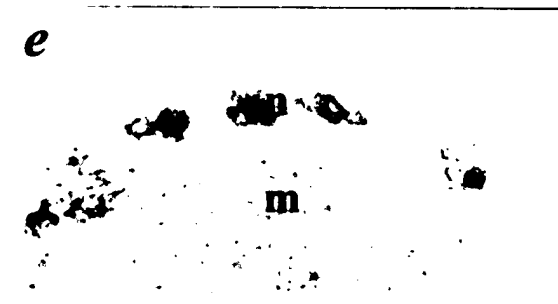
*FIG. 19B*



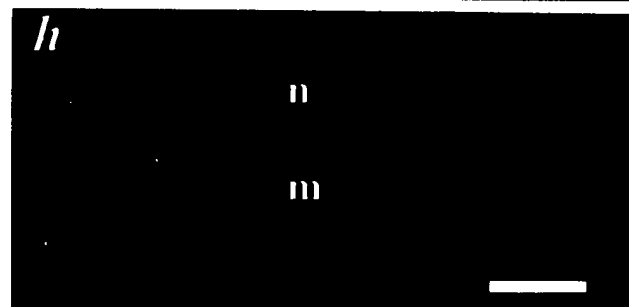
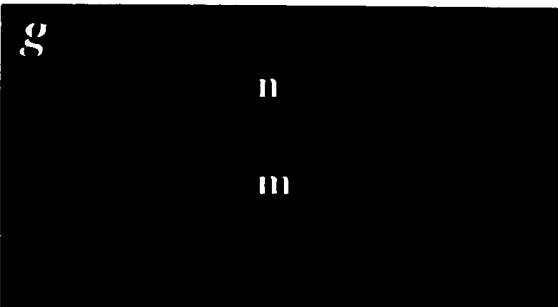
*FIG. 19C*

*FIG. 19D*

*FIG. 19E*



*FIG. 19F*

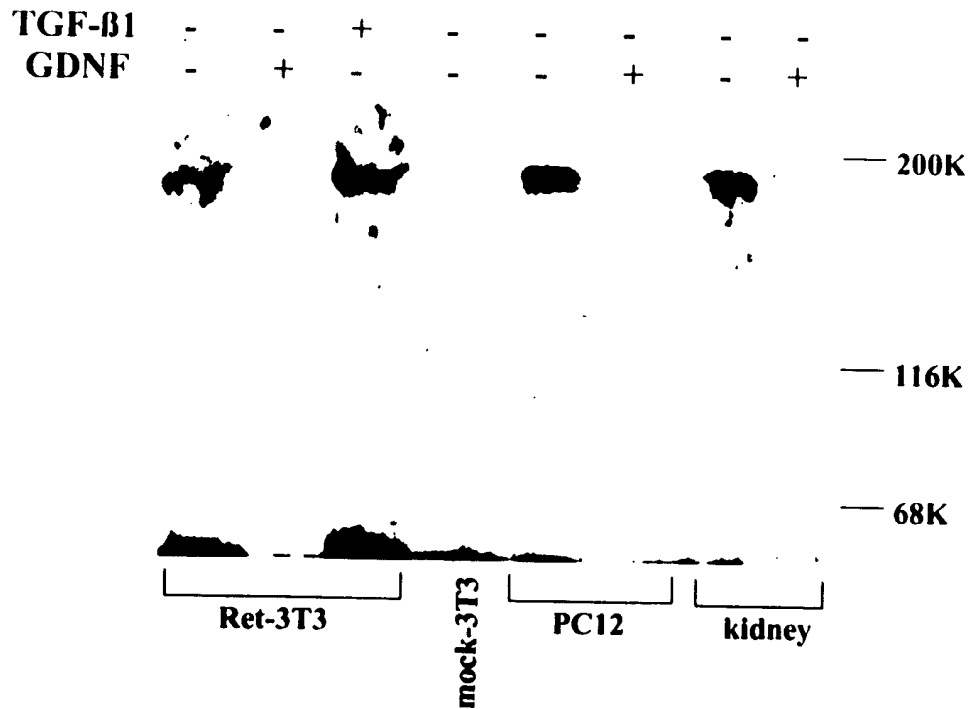
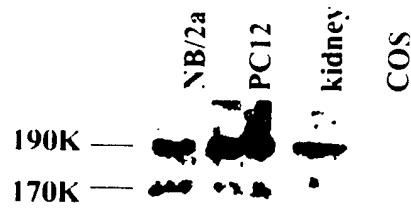


*FIG. 19G*

*FIG. 19H*

20/38

*FIG. 20A*

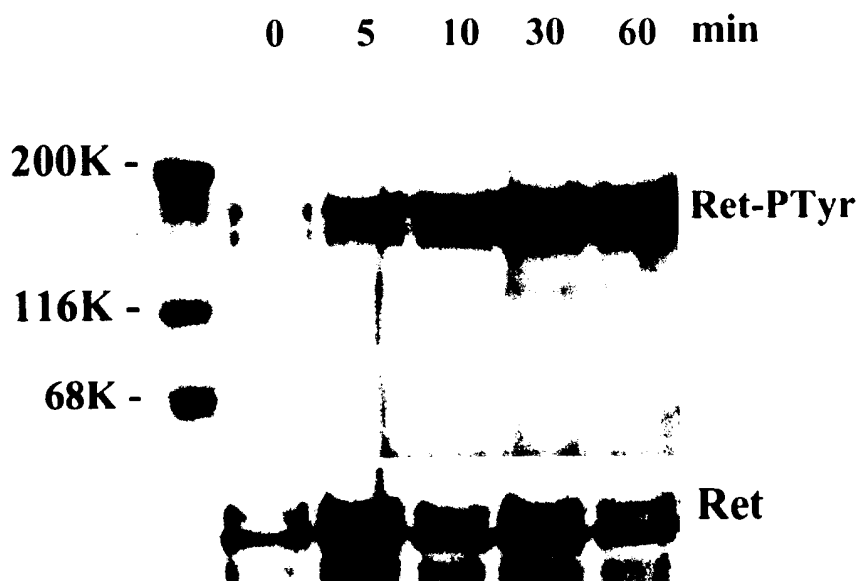
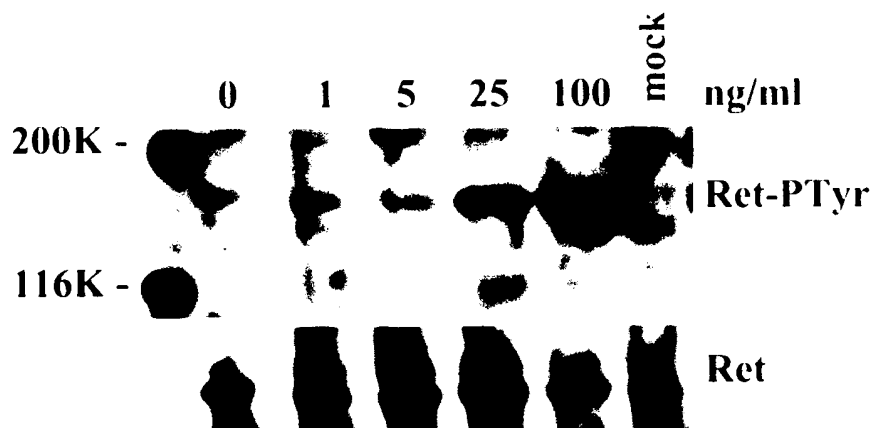


*FIG. 20B*

21/38

7

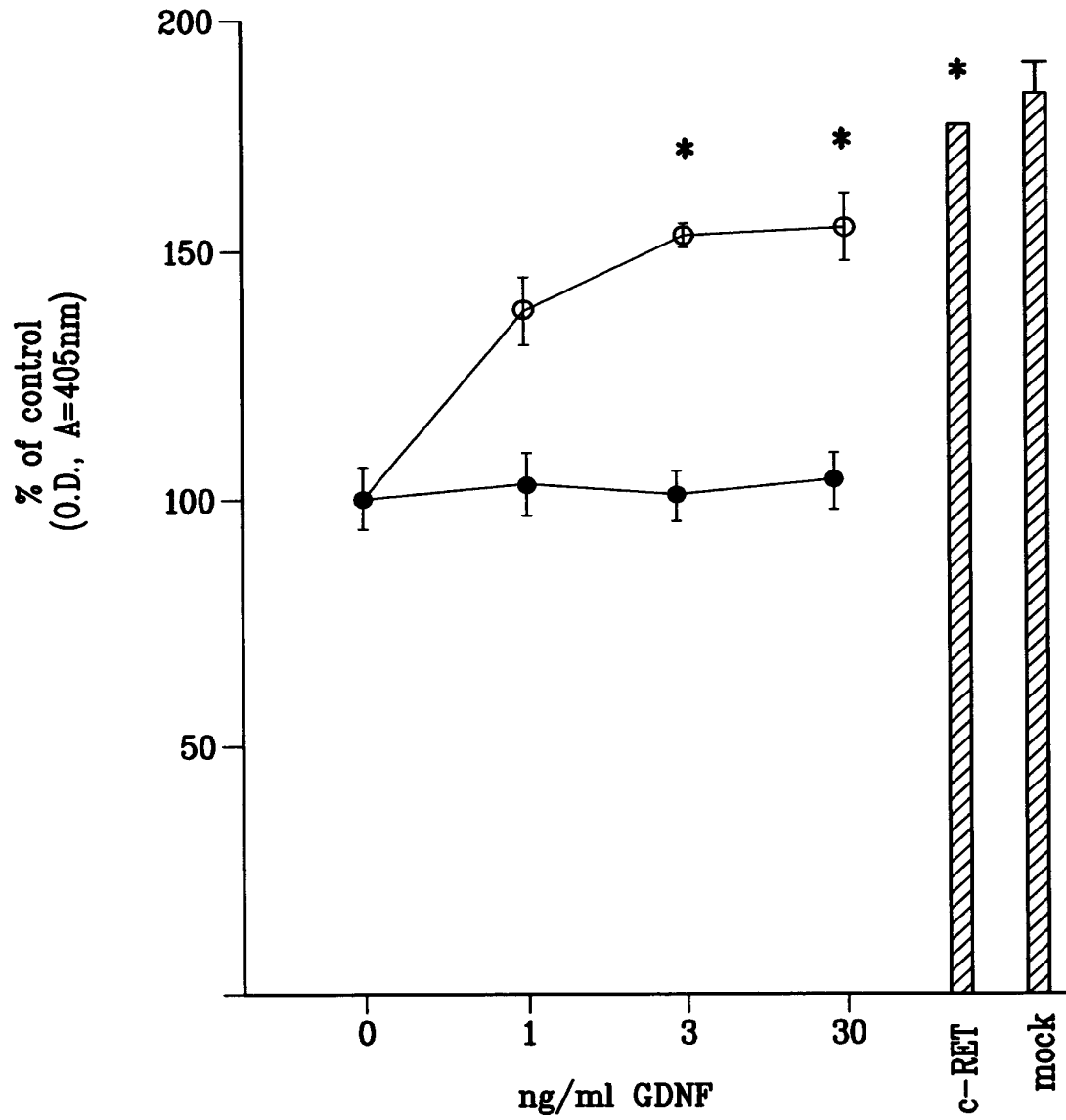
*FIG. 21A*



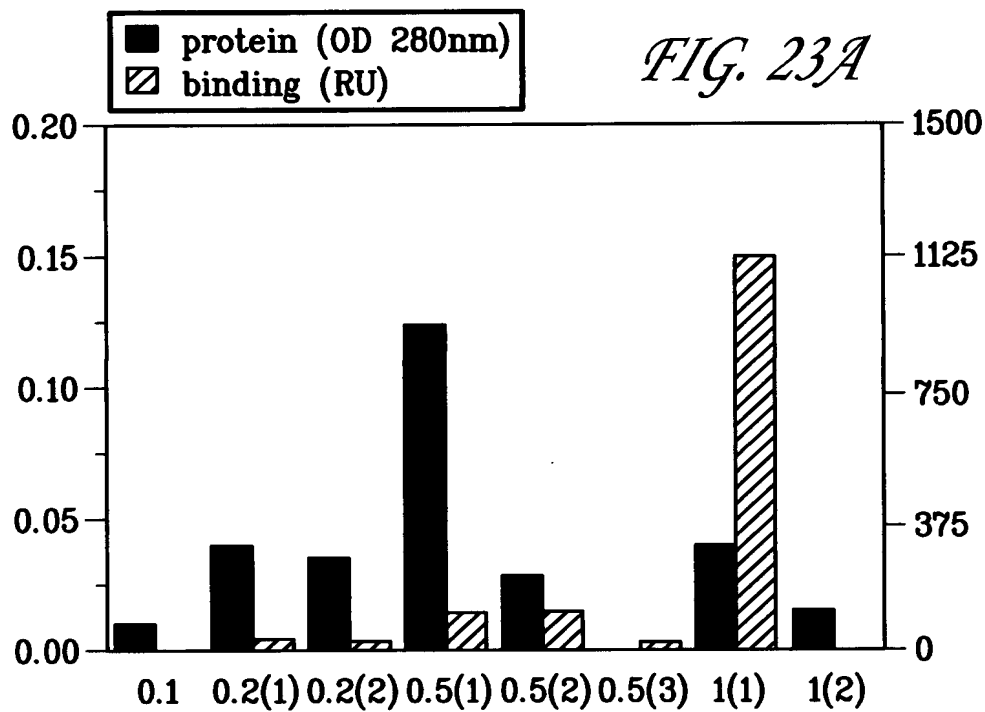
*FIG. 21B*

22/38

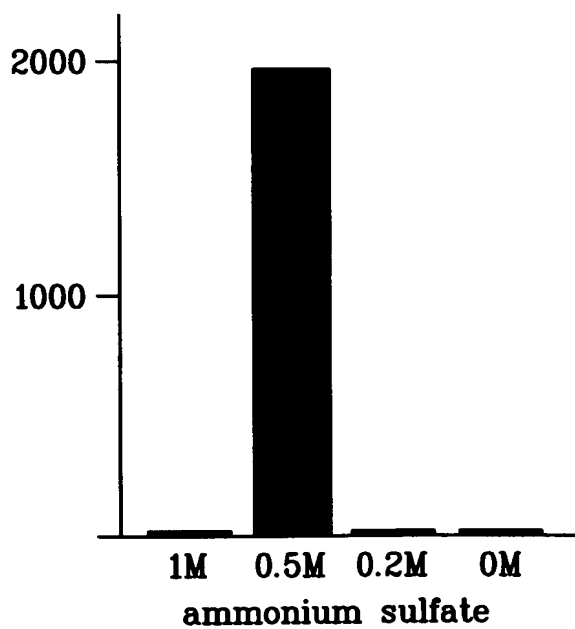
*FIG. 22*



23/38

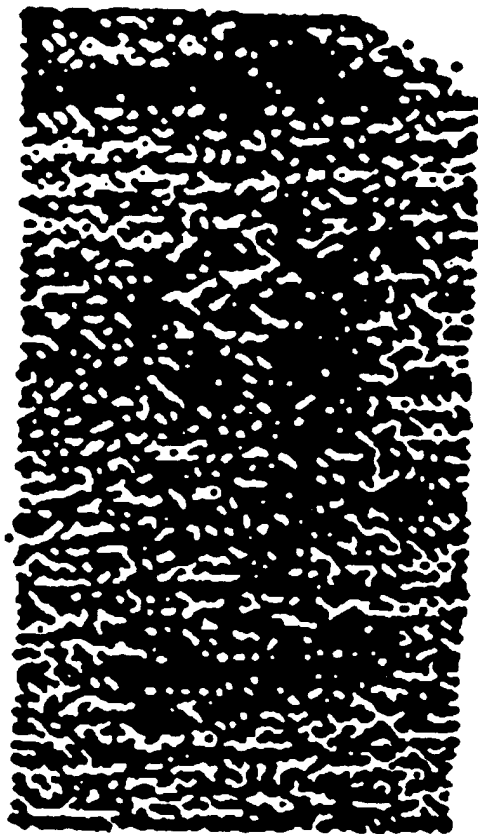


**FIG. 23B**



24/38

3 2 1



*FIG. 24*

201 kD

117 kD

82 kD

47 kD

*FIG. 25*

```

1  MILANAFCLF  FFLDETLRSL  ASPSSLQGSE  LHGWRPQVDC  VRANELCAAE
51  SNCSSRYRTL  RQCLAGRDRN  TMLANKECQA  ALEVLQESPL  YDCRCKRGMK
101 KELQCLQIYW  SIHLGLTEGE  EFYEASPYEP  VTSRLSDIFR  LASIFSGTGT
151 DPAVSTKSNH  CLDAAKACNL  NDNCKKLRS  YISICNREIS  PTERCNRRKC
201 HKALRQFFDR  VPSEYTYRML  FCSCQDQACA  ERRRQTILPS  CSYEDKEKPN
251 CLDLRLCRTL  DHLCRSLAD  FHANCRASYR  TITSCPADNY  QACLGSYAGM
301 IGFDMPNYV  DSNPTGIVVS  PWCNCRGSGN  MEECEKFLR  DFTENPCLRN
351 AIQAFNGTD  VMSPKGPSL  PATQAPRVEK  TPSLPDDLSD  STSLGTSVIT
401 TCTSIQEQGL  KANNSKELSM  CFTELTNIS  PGSKKVIKLN  SGSSRARLSA
451 ALTALPLML  TLAL  SEQ ID NO:2

```



25/38

GDNFR- $\beta$  1 MILANAFCLFFFLDETLRSLASPSSLQGSELHGWRPQVDCVRANELCAAE 50  
|:| | . : : : | | : . . . | . : . : : | | : | : | |  
GDNFR- $\alpha$  1 MFLATLYFALPLLDLLMSAEVSGGD.....RLDCVKASDQCLKE 39  
  
51 SNCSSRYRTL RQCLAGRDRN.....TMLANKECQA ALEBLQESPLYDCRC 95  
. | | : | | | | | : | | : | : : | . . | | . : | | : | | |  
40 QSCSTKYRTL RQC VAGKETNFSLTSGLEAKDECRS A MEALKQKSLYNCR C 89  
  
96 KRGMKKELQCLQIYWSYHLGLTEGEEFYEA SPYEPVTSRLSDIFRLASIF 145  
| | | | | | . | | . | | | : . : | : | : : . | . | | | | | . | | | | | | : : :  
90 KRGMKKEKNCLRIYWSMYQSL.QGNDLLEDSPYEPVNSRLSDIFRAVPFI 138  
  
146 SGTGTDPAVSTKSNHCLDAAKACNLNDNCKLRSSHISICNREISPTE RC 195  
| : . : . . | : | : | | | | | | | : | . | | . | | . | . : | . | |  
139 SDVFQQVEHISKGNCLDAAKACNLDDTCKKYRSAYITPCTTSMS.NEVC 187  
  
196 NRRKCHKALRQFFDRVPSEYTYRMLFCSCQDQACAERRRQTILPSCSYED 245  
| | | | | | | | | | : | | . . . | | | | | . | | . | | | | | : | | | :  
188 NRRKCHKALRQFFDKVPAKHSYGMLFCSCRDIAC TERRRQTIVPVCSYEE 237  
  
246 KEKPNCLDLRSLCRTDHLCSRSLADFHANCRASYRTITSCPADNYQACLG 295  
: | : | | | . | . . | : | : : | | | | | | . | | : . | . : . . | : | | . | |  
238 RERPNC LSLQDSCKTYNICRSLADFFTNCPESRSVSNCLKENYADCLL 287  
  
296 SYAGMIGFDMTPNYVDSNPTGIVVSPWCNCRGSGNMEEEECEKFLRDFTEN 345  
. | . | : | | | | | | | | : : : | . | | | : | . | | | | . | : |  
288 AYSGLIGTVMT PNYVDS..SSLSVAPWCD CSNSGNDLEDCLKFLNFFKTN 335  
  
346 PCLRNAIQAFNGGTDVNMS PKGPSLPATQAPRVEKTPSLPDDLSDSTS.. 393  
. | | : | | | | | | | . | | . | . . : | . : . . | | . . . . . | : . . . |  
336 TCLKNAIQAFNGGSDVTMWQPAPPVQTTTATTTTAFRVKNKPLGPAGSEN 385  
  
394 .LGTSVITTCTSIQE QGLKAN..NSKELSMCFTELTTNISPGSKKVIKLN 440  
: . | | : . . | . : | . | | | . | . | . : : : : : : : : | . . . | . .  
386 EIPTHVLPPCANLQAQKLKSNVSGSTHLCLSDSDFGKDGLAGASSHITTK 435  
  
441 SGSSRARLSAALTALPLIMLTAL\*..... 465 SEQ ID NO: 2  
| . | . | . . | | : | | | | |  
436 SMA..APPSCSLSSLPVLM L T.ALAALLSVSLEATS 468 SEQ ID NO: 1

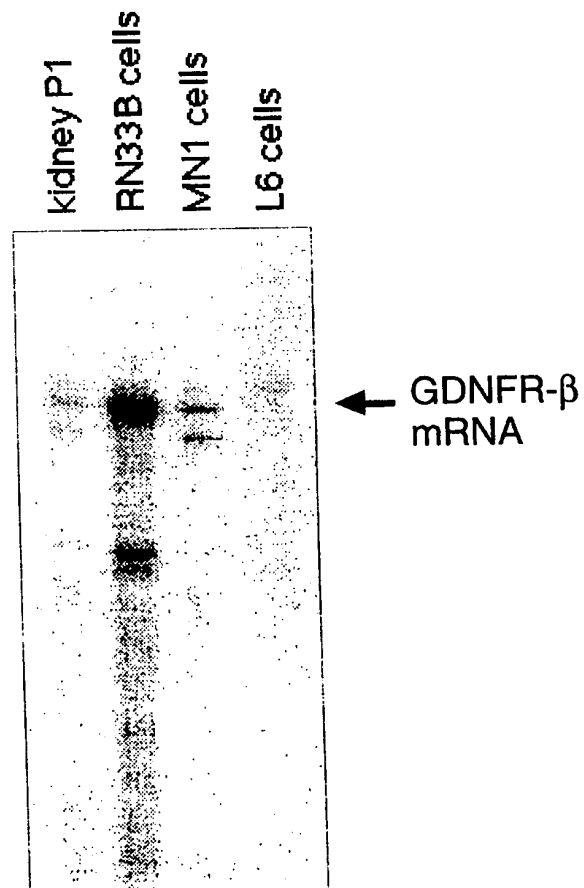
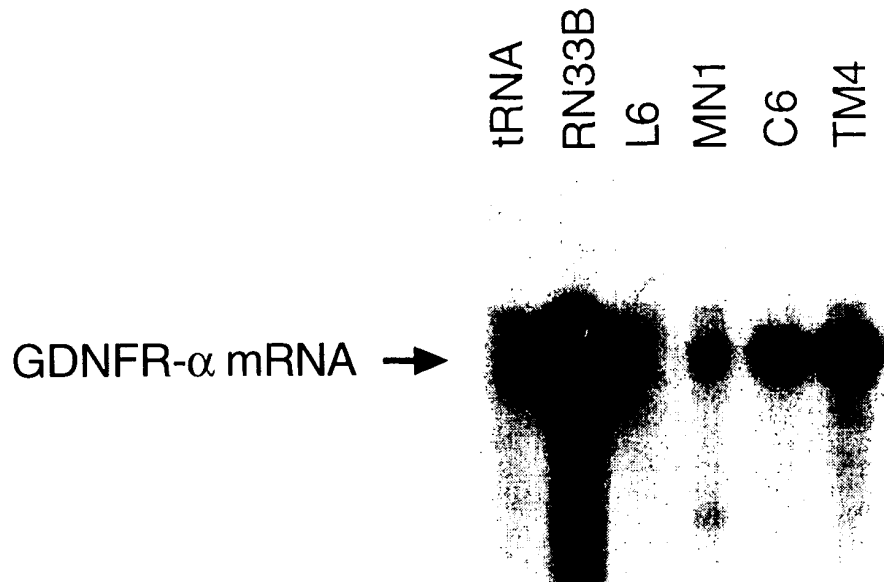
FIG. 26A

26/38

FIG. 26B

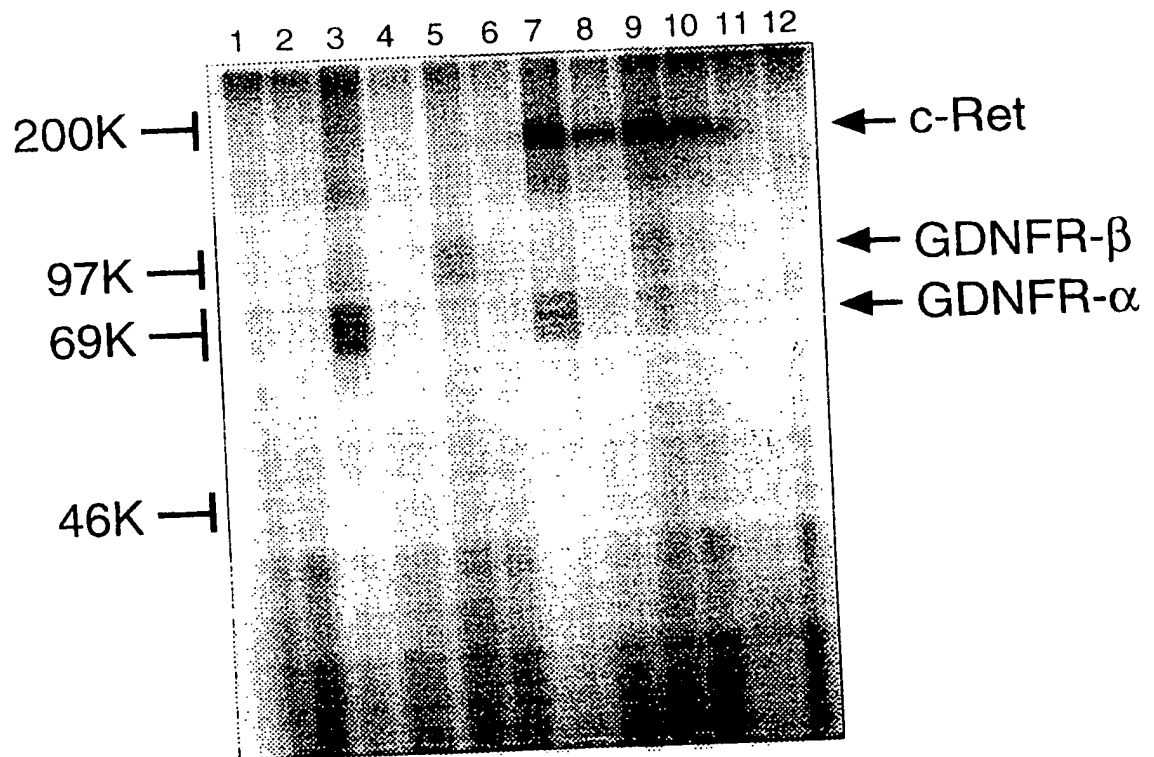
|          |  |                                    |     |
|----------|--|------------------------------------|-----|
| humalpha | MFLATLYFALPLDLLLSA.....EVSGGDRLLDCVKA  | SDQCLKEQSCSTKYRTLRCQVAGKETN        | 59  |
| ratalpha | <u>MFLATLYFALPLDLLMSA.....EVSGGDRLLDCVKA</u>                                       | <u>SDQCLKEQSCSTKYRTLRCQVAGKETN</u> | 59  |
| ratbeta  | MILANAFCLFFFLDETLRLASPSLQSGSELHGWRPQVDCVRANELCAAESNCSSRYRTLRCQLAGRDRN              |                                    | 70  |
| humbeta  | <u>MILANAFCLFFFLDETLRLASPSLQGPPELHGWRPPVDCVRANELCAAESNCSSRYRTLRCQLAGRDRN</u>       |                                    | 70  |
| humalpha | FSLASGLEAKDECRSAMEALKQKSLYNCRCRGMKEKNCRIYWSMYQSL.QGNDLLEDSPYEPVNSRL                |                                    | 128 |
| ratalpha | <u>FSLTSGLEAKDECRSAMEALKQKSLYNCRCRGMKEKNCRIYWSMYQSL.QGNDLLEDSPYEPVNSRL</u>         |                                    | 128 |
| ratbeta  | .....TMLANKECQAALEBLQESPLYDCRCRGMKEQLCQLIYWSYHLGLTEGEFFYEASPYEPTVTSRL              |                                    | 135 |
| humbeta  | <u>.....TMLANKECQAALEBLQESPLYDCRCRGMKEQLCQLIYWSYHLGLTEGEFFYEASPYEPTVTSRL</u>       |                                    | 135 |
| humalpha | SDIFRVVPFISDVFOQVEHIPKGNNCILDAKACNLDDICKKYRSAYITPCTTSVS.NDVNCRRKCHKALR             |                                    | 198 |
| ratalpha | <u>SDIFRAVPFISDVFOQVEHISKGNNCILDAKACNLDDTCKKYRSAYITPCTTSMS.NEVCNRRKCHKALR</u>      |                                    | 198 |
| ratbeta  | SDIFRLASIFSGTGTDPAVSTKSNHCLDAKACNLNDNCKLRSSYISICNREISPTERCNRRKCHKALR               |                                    | 205 |
| humbeta  | <u>SDIFRLASIFSGTGADPVVSAKSNHCLDAKACNLNDNCKLRSSYISICNREISPTERCNRRKCHKALR</u>        |                                    | 205 |
| humalpha | QFFDKVPAKHSYGMFLFCSCRDIACTERRRQTIIVPVCSEEREKPNCLSLQDSCKTNYICRSRLADFFTNC            |                                    | 268 |
| ratalpha | <u>QFFDKVPAKHSYGMFLFCSCRDIACTERRRQTIIVPVCSEEREKPNCLSLQDSCKTNYICRSRLADFFTNC</u>     |                                    | 268 |
| ratbeta  | QFFDRVPSEYTYRMLFCSCQDQACAERRRQTIILPSCSYEDEKPNCLDLRLSCLRTDHLCRSRLADFHANC            |                                    | 275 |
| humbeta  | <u>QFFDRVPSEYTYRMLFCSCQDQACAERRRQTIILPSCSYEDEKPNCLDLRGVCRDTHLCSRLADFHANC</u>       |                                    | 275 |
| humalpha | QPESRSVSSCLKENYADCLLAYSGLIGTVMTPNYIDSS...SLSVAPWPCDCNSGNDLEECCLKFLNFFKDN           |                                    | 336 |
| ratalpha | <u>QPESRSVSNCLKENYADCLLAYSGLIGTVMTPNYVDSS...SLSVAPWPCDCNSGNDLEDCCLKFLNFFKDN</u>    |                                    | 336 |
| ratbeta  | RASYRTITSCPADNYQACLSYAGMIGFDMTPNYVDNPTGIVVSPWCNCRGSGNMEEECEKFLRDRFTEN              |                                    | 345 |
| humbeta  | <u>RASYQTVTSCPADNYQACLSYAGMIGFDMTPNYVDSSPTGIVVSPWCNCRGSGNMEEECEKFLRDRFTEN</u>      |                                    | 345 |
| humalpha | TCLKNAIQAFNGSGDVTVWQPAFPVQTTTATTTALRVKNKPLGPAGSENEIPTHVLPCCANLQAQKLKS              |                                    | 406 |
| ratalpha | <u>TCLKNAIQAFNGSGDVTVWQPAFPVQTTTATTTAFRVKNKPLGPAGSENEIPTHVLPCCANLQAQKLKS</u>       |                                    | 406 |
| ratbeta  | PCLRNAIQAFNGNGTDVNMSPKGPSPATQA PRVEKTPSLPDDLS DSTS...LGTSVITTTCTSIQEQGLKA          |                                    | 412 |
| humbeta  | <u>PCLRNAIQAFNGNGTDVNVSPKGPSPFQATQA PRVEKTPSLPDDLS DSTS...LGTSVITTTCTSVQEQGLKA</u> |                                    | 412 |
| humalpha | NVSGNTHLCISNGNYEKEGL.GASSHITTKSMA..APPSGCLSPLLVRVWTALSTLL..SLTETS*                 |                                    | 465 |
| ratalpha | <u>NVSGSTHLCILSDSDFGKDGLAGASSHITTKSMA..APPCSLSLPLVIMLTALAAALLSVSLEATS*</u>         |                                    | 465 |
| ratbeta  | NNSKELSMCFTE..LTTNISP GSKVKIKLNSGSSL.....  |                                    | 445 |
| humbeta  | <u>NNSKELSMCFTE..LTTNIIIPGSNKV I KPNSGSSRARPSAALT VLSVIMLKQAL*</u>                 |                                    | 464 |

27/38



28/38

*FIG. 29*

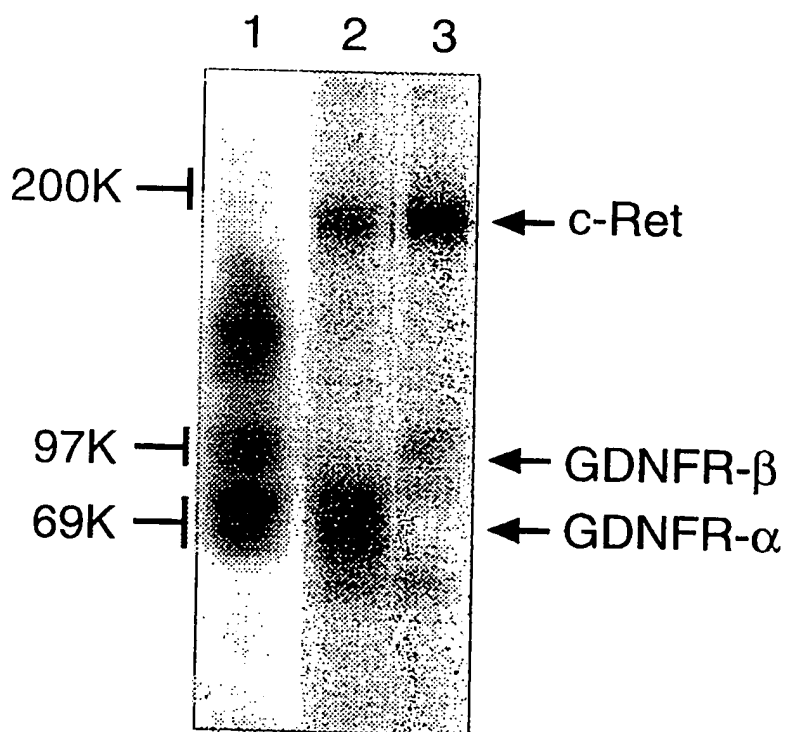


- 1: control plasmid
- 2: control plasmid + cold
- 3: GDNFR- $\alpha$
- 4: GDNFR- $\alpha$  + cold
- 5: GDNFR- $\beta$
- 6: GDNFR- $\beta$  + cold
- 7: c-Ret + GDNFR- $\alpha$
- 8: c-Ret + GDNFR- $\alpha$  + cold
- 9: c-Ret + GDNFR- $\beta$
- 10: c-Ret + GDNFR- $\beta$  + cold
- 11: c-Ret
- 12: c-Ret + cold

29/38

7

*FIG. 30*

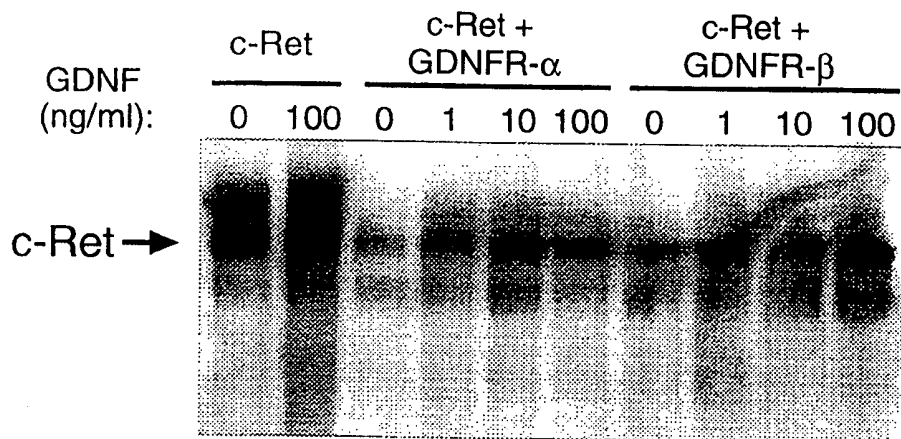


- 1: RN33B  
2: COS transfected with Ret and GDNFR- $\alpha$   
3: COS transfected with Ret and GDNFR- $\beta$

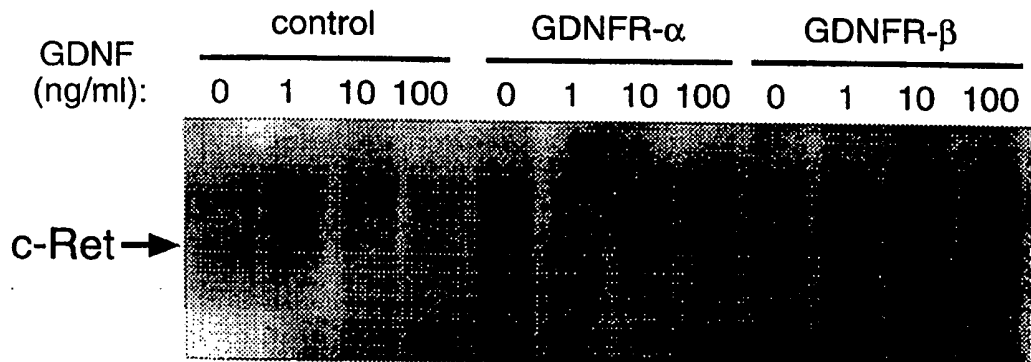
30/38

# FIG. 31

COS cells transfected with c-Ret and GDNFR- $\alpha$  or GDNFR- $\beta$  cDNAs



Neuro-2A cells transfected with GDNFR- $\alpha$  or GDNFR- $\beta$  cDNAs



31/38

*FIG. 32*

1 ATGATCTTGG CAAACGCCTT CTGCCTCTTC TTCTTTTTTAG ACGAAACCCT  
51 CCGCTCTTTG GCCAGCCCTT CCTCCCTGCA GGGCTCTGAG CTCCACGGCT  
101 GGCGCCCCCA AGTGGACTGT GTCCGGGCCA ATGAGCTGTG TGGGGCTGAA  
151 TCCAACCTGCA GCTCCAGGTA CCGCACCCCTT CGGCAGTGCC TGGCAGGCCG  
201 GGATCGCAAT ACCATGCTGG CCAATAAGGA GTGCCAGGCA GCCCTGGAGG  
251 TCTTGCAGGA AAGCCCACTG TATGACTGCC GCTGCAAGCG GGGCATGAAG  
301 AAGGAGCTGC AGTGTCTGCA GATCTACTGG AGCATCCATC TGGGGCTGAC  
351 AGAGGGTGAG GAGTTCTATG AAGCTTCCCC CTATGAGCCT GTGACCTCGC  
401 GCCTCTCGGA CATCTTCAGG CTCGCTTCAA TCTTCTCAGG GACAGGGACA  
451 GACCCGGCAG TCAGTACCAA AAGCAACCAC TGCCTGGATG CCGCCAAGGC  
501 CTGCAACCTG AATGACAACCT GCAAGAAGCT TCGCTCCTCT TATATCTCCA  
551 TCTGCAACCG TGAGATCTCT CCCACCGAAC GCTGCAACCG CCGCAAGTGC  
601 CACAAGGCTC TGCGCCAGTT CTTTGACCGT GTGCCCAGCG AGTATACCTA  
651 CCGCATGCTC TTCTGCTCCT GTCAGGACCA GGCATGTGCT GAGCGTCGCC  
701 GGCAAACCAT CCTGCCCAGT TGCTCCTATG AGGACAAGGA GAAGCCCCAAC  
751 TGCCTGGACC TGCGCAGCCT GTGTCGTACA GACCACCTGT GCCGGTCCCG  
801 ACTGGCAGAT TTCCACGCCA ACTGTCGAGC CTCCTACCGG ACAATCACCA  
851 GCTGTCCTGC GGACAACCTAC CAGGCATGTC TGGGCTCCTA TGCTGGCATG  
901 ATTGGGTTTG ATATGACACC CAACTATGTG GACTCCAACC CCACGGGCAT  
951 CGTGGTGTCT CCCTGGTGCA ATTGTCGTGG CAGTGGGAAC ATGGAAGAAG  
1001 AGTGTGAGAA GTTCCTCAGG GACTTCACGG AAAACCCATG CCTCCGGAAT  
1051 GCCATTCAGG CCTTTGGTAA TGGCACAGAT GTGAACATGT CTCCCAAAGG  
1101 CCCCTCACTC CCAGCTACCC AGGCCCTCG GGTGGAGAAG ACTCCTTCAC  
1151 TGCCAGATGA CCTCAGTGAC AGCACCAGCC TGGGGACCAG TGTCATCACC  
1201 ACCTGCACAT CTATCCAGGA GCAAGGGCTG AAGGCCAACA ACTCCAAAGA  
1251 GTTAAGCATG TGCTTCACAG AGCTCACGAC AAACATCAGT CCAGGGAGTA  
1301 AAAAGGTGAT CAAACTTAAC TCAGGCTCCA GCAGAGCCAG ACTGTCTGGCT  
1351 GCCTTGACTG CCCTCCCCT CCTGATGCTG ACCTTGGCCT TGTAGGCCTT  
1401 TGAACCCAG CACA SEQ ID NO: 5

32/38

5' **ATGATCTTGGCAACGCCCTTCTG**CCCTCTTCTTCTTTCTAGACGAGACCCCTCCGCTCTTTGGCCAGCCCTTCTCCTCCCTGCA 80  
GGCCCCGAGCTCCACGGCTGGCGCCCCCAGTGGAAGTGTCCGGCCAAATGAGCTGTGTGCCGCCGGAATCCAACCTGCA 160  
GCTCTCGCTACCGCACTCTGCGCAGTGCCTGGCAGGCCCGGACCGCAACACCATGCTGGCCAAACAAGGAGTGCCAGGCG 240  
GCCTTGGAGGTCCTGCAGGAGAGCCCCGCTGTACGACTGCCGCTGCAAGCGGGGCATGAAGAAGGAGCTGCAGTGTCTGGA 320  
GATCTACTGGAGCATCCACCTGGGGCTGACCGAGGGTGAGGAGTTCTACGAAGCCTCCCCCTATGAGCCGGTGACCTCCC 400  
GCCCTCGGACATCTTCAGGCTTGCTTCAATCTTCTCAGGGACAGGGGCAGACCCGGTGGTCAGCGCCAAAGAGCAACCAT 480  
TGCCTGGATGCTGCCAAGGCC**TGCAACCTGAATGACAACCTGCAA**GAAGCTGCGCTCCTCCTACATCTC**CATCTGCA**ACCG 560  
CGAGATCTCGCCCAACGAGCGCTGCAACCGCCGCAAGTGCCACAAGGCCCTGGCCAGTTCTTCGACCCGGTGCCCAAGCG 640  
AGTACACCTACCGCATGCTCTTCTGCTCCTGCCAAGACCAAGCGGTGCGCTGAGCGCCCGCGCAACCATCTCTGCCCAGC 720  
TGCTCCTATGAGGACAAGGAGAAGCCCCAACTGCCCTGGACCTGCGTGCGGTGTGCCGGAAGTACCACTGTGTGGTCCCG 800  
GCTGGCCGACTTCCATGCCAATTGTCGAGCCTCCTACGACGGTCAACGCTGCCCTGGGACAATTACCAGGCGTGTCC 880  
TGGGCTCTTATGCTGGCATGATTGGGTTTGACATGACACCTAACTATGTGGACTCCAGCCCCACTGGCATCGTGGTGTCC 960  
CCCTGGTGCAGCTGTCTGTGGCAGCGGGAACATGGAGGAGGAGTGTGAGAAAGTTCTCAGGGACTTCAACGAGAACCCATG 1040  
CCTCCGGAACGCCATCCAGGCCTTTGGCAACGGCACGGACGTGAACGTGTCCCCAAAGGCCCTCGTTCAGGGCCACCC 1120  
AGGCCCTCGGGTGGAGAAAGCGCCTTCTTTGCCAGATGACCTCAGTGACAGTACCAGCTTGGGACCAAGTGTATCACC 1200  
ACCTGCACGCTGTCTCCAGGACAGGGGCTGAAGGCCCAACAACCTCCAAAGAGTTAAGCATGTGCTTACAGAGCTCACGAC 1280  
AAATATCATCCCAGGGAGTAACAAGGTGATCAAACTTAAGTCAAGCCCCAGAGCCGACAGCCGTCGGCTGCCCTTGACCG 1360  
TGCTGTCTGTCTGATGCTGAACAGGCCCT**TGTA**GGCTGTGGGAACCGAGTCAGAAAGATTTTGAAACTACGCAGACAAG 1440  
AACAGCCGCCTGACGAAATGGAAACACACACAGACACACACCTTGC-3' 1490

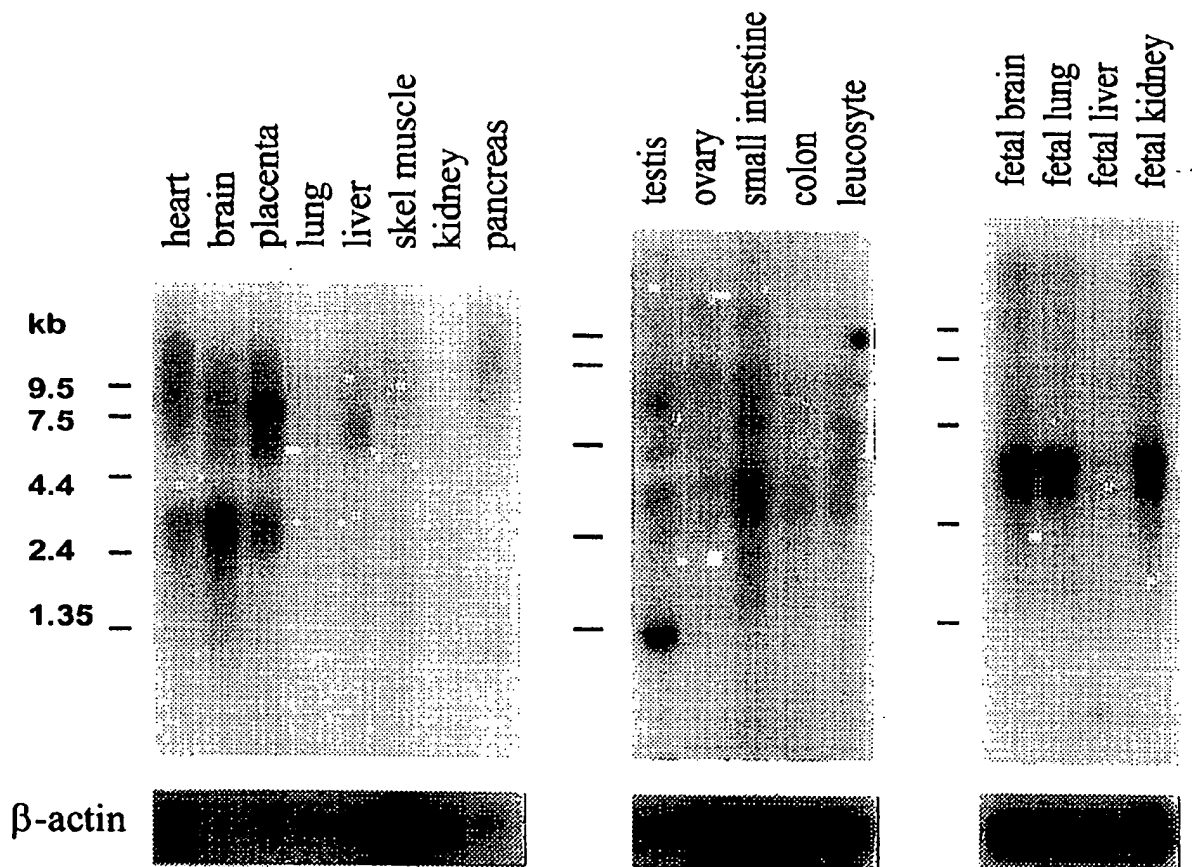
SEQ ID NO.:10

FIG. 33



33/38

*FIG. 34*



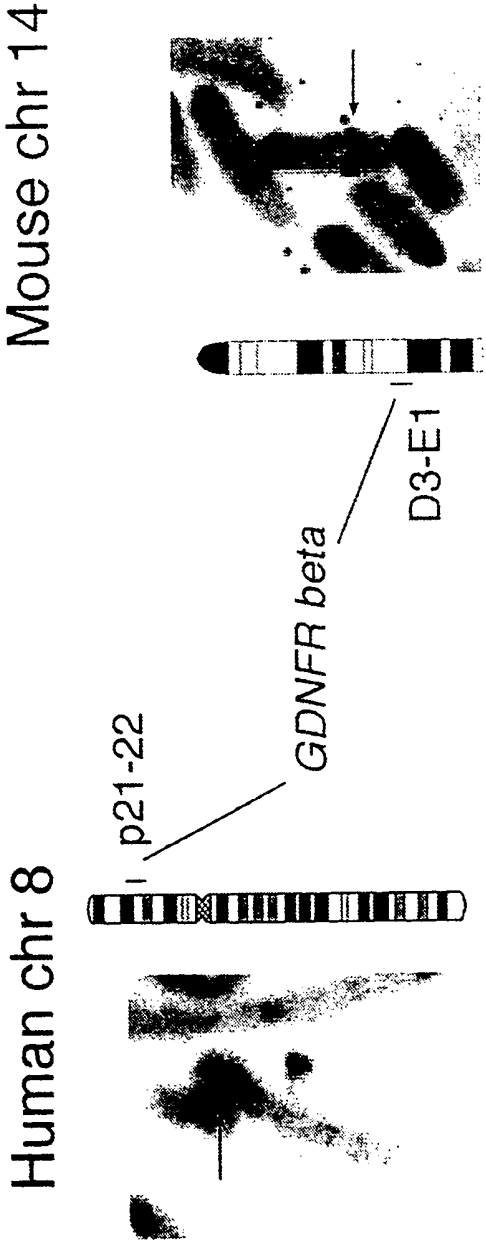


FIG. 35

35/38

*FIG. 36*

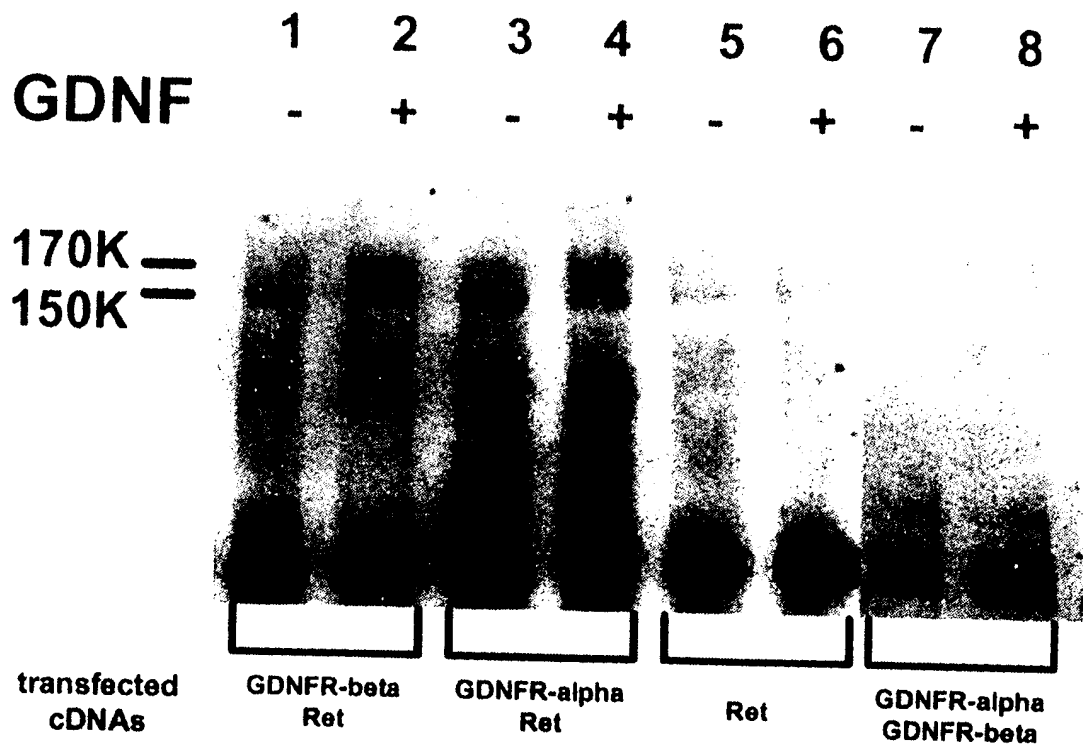


FIG. 37A



FIG. 37B



FIG. 37C



FIG. 37D



FIG. 37E

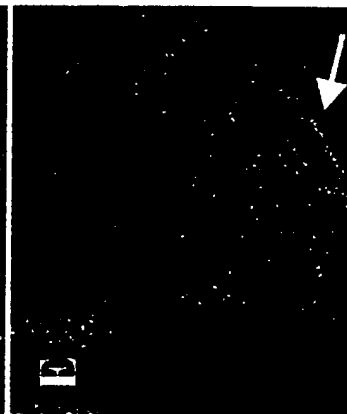
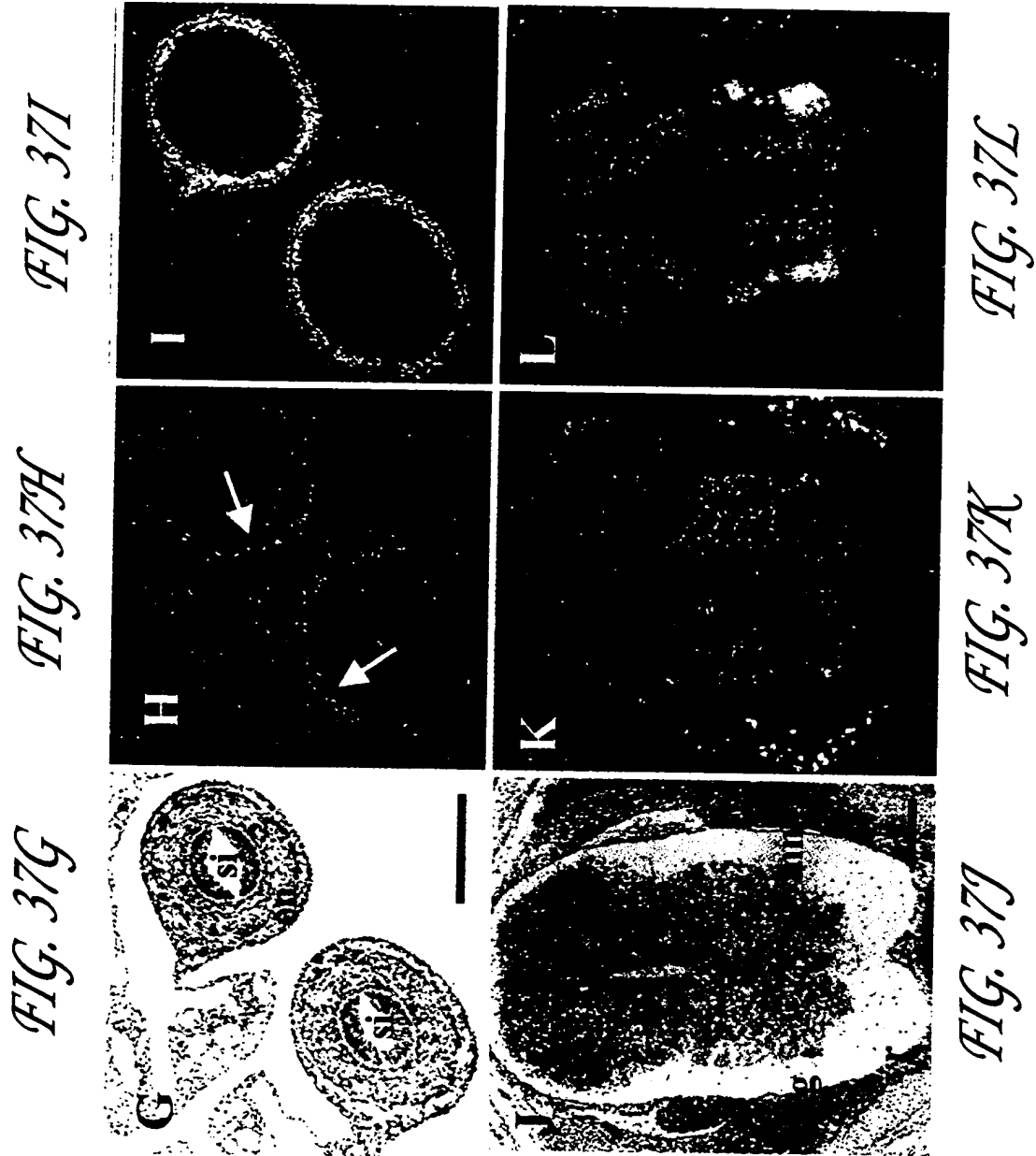


FIG. 37F





38/38

7

*FIG. 37O*



*FIG. 37N*



*FIG. 37M*

